

*Forum Minireview*

## Analysis of the Mechanism for the Development of Allergic Skin Inflammation and the Application for Its Treatment: Mouse Models for the Development of Remedies for Human Allergic Dermatitis

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**Abstract.** Animal models for human diseases are important for the elucidation of mechanisms involved in as well as for the establishment of effective treatment strategies for the diseases. Many mouse allergic dermatitis models have been established and applied for the development of remedies for human allergic dermatitis. One of the simplest allergic cutaneous reaction models is passive cutaneous anaphylaxis. Skin mast cells passively sensitized with antigen-specific IgE are activated upon antigen challenge to cause vascular permeability increase. The triphasic cutaneous reaction is another interesting model in which triphasic cutaneous swelling appears in mice passively sensitized with IgE upon challenge with specific antigen. Recently, many allergic dermatitis models have been established by repeated antigen exposure. Although the induced dermatitis seems to be complex, these models may possess the characteristic features observed in patients. Naturally occurring dermatitis model mice such as NC/Nga, NOA, and DS-Nh mice, and gene-knockout and transgenic mice exhibiting spontaneous dermatitis are also known. Establishment and characterization of the mouse dermatitis models seem to be important for understanding dermatitis and development of new strategies for the treatment of these diseases.

**Keywords:** mouse model, allergic dermatitis, IgE, mast cell, Th2, allergic inflammation

### Introduction

Animal models for human diseases are very important for examining the mechanisms involved in as well as for constructing treatment strategies for the diseases. Many animal models have been established and utilized widely. Animal models are divided into 2 groups: One is naturally occurring and the other is artificially induced. Naturally occurring models are usually based on mutations and are sometimes difficult to discover. Recently, gene-knockout and transgenic mice can be easily prepared. Some gene-altered mice are known to be interesting models for human diseases.

Many animal models for human allergic dermatitis have also been established. Artificially induced allergic

dermatitis models may be subdivided into 2 groups, passively sensitized and actively sensitized. Although actively sensitized models may reflect some aspects of human diseases, the underlying mechanisms seem to be complex. In contrast, passively sensitized models may be simple and useful for examining a defined mechanism. Furthermore, gene-altered mice that exhibit allergic dermatitis spontaneously are also considered to be artificially induced models. These models and naturally occurring models have widely been used for developing anti-allergic drugs. Some mouse models useful for the study of allergic dermatitis, especially for atopic dermatitis, are listed in Table 1.

In the present paper, we describe established animal models for allergic dermatitis, mainly focusing on models that we have employed in our studies.

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**Table 1.** Mouse allergic dermatitis models and their references

|                                                                                               |                                                                |
|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Naturally occurring                                                                           |                                                                |
| NC/Nga mouse                                                                                  | Matsuda H et al, <i>Int Immunol</i> 1997 (27)                  |
| NOA mouse                                                                                     | Kondo T et al, <i>Mouse Genome</i> 1997 (29)                   |
| DS-Nh mouse                                                                                   | Watanabe A et al, <i>Exp Anim</i> 2003 (30)                    |
| Artificially induced                                                                          |                                                                |
| Passively sensitized                                                                          |                                                                |
| passive cutaneous anaphylaxis in the mouse ear                                                | Inagaki N et al, <i>Int Arch Allergy Appl Immunol</i> 1984 (4) |
| triphasic cutaneous reaction                                                                  | Tahara E et al, <i>Allergol Int</i> 1999 (17)                  |
| Actively sensitized                                                                           |                                                                |
| active cutaneous anaphylaxis in the mouse ear                                                 | Inagaki N et al, <i>Jpn J Pharmacol</i> 1992 (11)              |
| repeated exposure to trinitrochlorobenzene (TNCB)                                             | Kitagaki H et al, <i>J Invest Dermatol</i> 1995 (21)           |
| repeated exposure to dinitrofluorobenzene (DNFB)                                              | Nagai H et al, <i>J Pharmacol Exp Ther</i> 1997 (23)           |
| repeated exposure to mite antigen in NC/Nga mouse                                             | Gao XK et al, <i>Biol Pharm Bull</i> 2004 (28)                 |
| Gene-altered (gene-knockout and transgenic)                                                   |                                                                |
| human apolipoprotein C1 (APOC1)-transgenic mouse                                              | Jong MC et al, <i>J Clin Invest</i> 1998                       |
| RelB-knockout mouse                                                                           | Barton D et al, <i>Eur J Immunol</i> 2000                      |
| human caspase 1 (CASP1)-transgenic mouse (keratinocyte-specific)                              | Yamanaka K et al, <i>J Immunol</i> 2000                        |
| IL-4-transgenic mouse (keratinocyte-specific)                                                 | Chan JS et al, <i>J Invest Dermatol</i> 2001                   |
| IL-18-transgenic mouse (keratinocyte-specific)                                                | Konishi H et al, <i>Proc Natl Acad Sci USA</i> 2002            |
| cathepsin E (CatE)-knockout mouse                                                             | Tsukuba T et al, <i>J Biochem</i> 2003                         |
| bacterial artificial chromosome (BAC; including IL-4, IL-5, and IL-13 genes)-transgenic mouse | Lee GR, <i>Immunity</i> 2003                                   |
| I $\kappa$ B $\zeta$ -knockout mouse                                                          | Shiina T et al, <i>J Biol Chem</i> 2004                        |
| thymic stromal lymphopoietin (TSLP)-transgenic mouse                                          | Yoo J et al, <i>J Exp Med</i> 2005                             |
| IL-13-transgenic mouse                                                                        | Zheng T et al, <i>J Invest Dermatol</i> 2009                   |
| Others                                                                                        |                                                                |
| HR-1 mouse (special diet feeding)                                                             | Fujii M et al, <i>Exp Dermatol</i> 2005                        |

### Passive cutaneous anaphylaxis in the mouse ear

Passive cutaneous anaphylaxis (PCA) is one of the simplest allergic cutaneous reactions *in vivo*. The IgE-mediated mast cell activation is evaluated by vascular permeability increase. The technique of PCA was established by Ovary in the 1950s (1, 2). Skin mast cells are passively sensitized with intradermally injected IgE and stimulated with intravenously injected specific antigen. Activated mast cells release vasoactive mediators and vascular permeability increase appearing immediately after antigen challenge is visualized by extravasation of dye given simultaneously with antigen. Not only IgE but also IgG can induce PCA in many animal species, and rat IgE-mediated homologous PCA has frequently been used for evaluating anti-allergic compounds.

In 1961, Feinberg reported that the mouse ear is suitable for eliciting PCA (3). According to the report, we established a protocol for inducing PCA in the mouse ear and a method for evaluating extravasated dye into the

ear (Fig. 1A) (4, 5). Antiserum containing IgE or monoclonal IgE at an appropriate dilution in a volume of 10  $\mu$ l is injected into the mouse ear for passive sensitization. At an appropriate period after the sensitization, PCA is evoked by injecting specific antigen with Evans blue dye intravenously. Extravasated dye is extracted and measured colorimetrically at 620 nm. The bluing reaction in the mouse ear by PCA is shown in Fig. 1C.

Ear PCA can be induced in many strains of mice and the reaction is more sensitive and reproducible than that in the dorsal skin (6). It is interesting to note that nude mice exhibit clear dorsal skin PCA almost comparable to that in the ear. Histamine, serotonin, leukotriene (LT) C<sub>4</sub>, and LTD<sub>4</sub> induce vascular permeability increase; and prostaglandin (PG) E<sub>1</sub> potentiates vascular permeability increase caused by other mediators in the mouse ear. However, histamine seems to be the most important vascular permeability increasing factor in the mouse ear PCA (7). Monoclonal IgG1 can induce PCA similar to the case of IgE, although sensitization with IgG1 disappears within 72 h. In contrast, once sensitized with

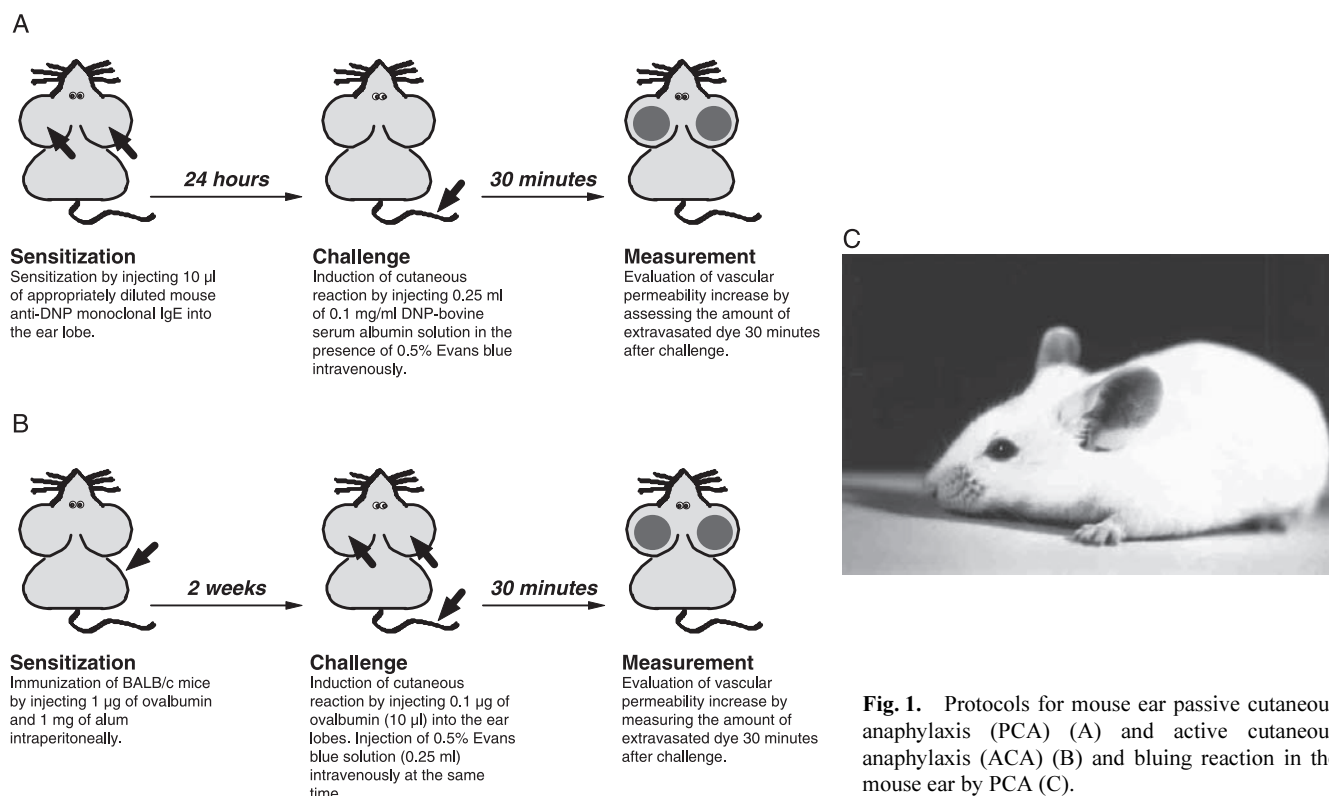


**Fig. 1.** Protocols for mouse ear passive cutaneous anaphylaxis (PCA) (A) and active cutaneous anaphylaxis (ACA) (B) and bluing reaction in the mouse ear by PCA (C).

IgE, PCA can be induced even after 7 days (8). PCA mediated with both IgE and IgG1 is mast cell-dependent.

If mice are sensitized simultaneously with monoclonal IgE and IgG1 with different antigen specificities, IgE- and IgG1-mediated PCA can be observed in the same mouse. The first PCA is evoked without Evans blue dye and the second is evoked with Evans blue dye to visualize the reaction at an appropriate interval. If IgE-PCA is induced first, the following IgG1-PCA is completely abrogated. In contrast, elicitation of IgG1-PCA does not affect the following IgE-PCA (9). These results strongly suggest that the alteration of skin mast cells is minimal in IgG1-PCA compared to that in IgE-PCA, when reactions with a similar intensity are evoked. It is further suggested, therefore, that the small reaction of mast cells initiated by IgG1 might be potentiated by another mechanism in IgG1-PCA. Actually, an antagonist against platelet activating factor (PAF) inhibits IgG1-PCA, although it fails to affect IgE-PCA (10). Therefore, PAF may be involved in IgG1-PCA. Participation of PAF in IgG1-PCA may explain the difference between IgE-PCA and IgG1-PCA.

Mouse ear PCA is a useful model for the examination of mast cell activation *in vivo* and for the evaluation of anti-allergic compounds (5).

### Active cutaneous anaphylaxis in the mouse ear

Active cutaneous anaphylaxis (ACA) is another model for evaluating skin mast cell activation. Mast cells are sensitized with IgE produced by the host animals and stimulated by injecting specific antigen intradermally. If a dye is injected intravenously at the same time, vascular permeability increase caused by mast cell mediators can be visualized.

We established a protocol for inducing ACA in the mouse ear (11) (Fig. 1B). Dye extravasation is evaluated similarly to the case in PCA. Female BALB/c mice are immunized with ovalbumin (OVA) in the presence of aluminum hydroxide gel to induce IgE production. The BALB/c strain of mice is a higher responder strain for IgE production, and female mice are known to produce a larger amount of IgE than male mice. Two weeks after the immunization, ACA is elicited in the mouse ear by injecting 10  $\mu$ l of antigen solution into the ear lobe. ACA is assessed by the amount of extravasated dye, which is given intravenously immediately after the antigen injection.

As ACA involves a process from IgE production to IgE-mediated skin mast cell activation, IgE production inhibitors as well as mast cell stabilizers and mediator inhibitors can be evaluated.

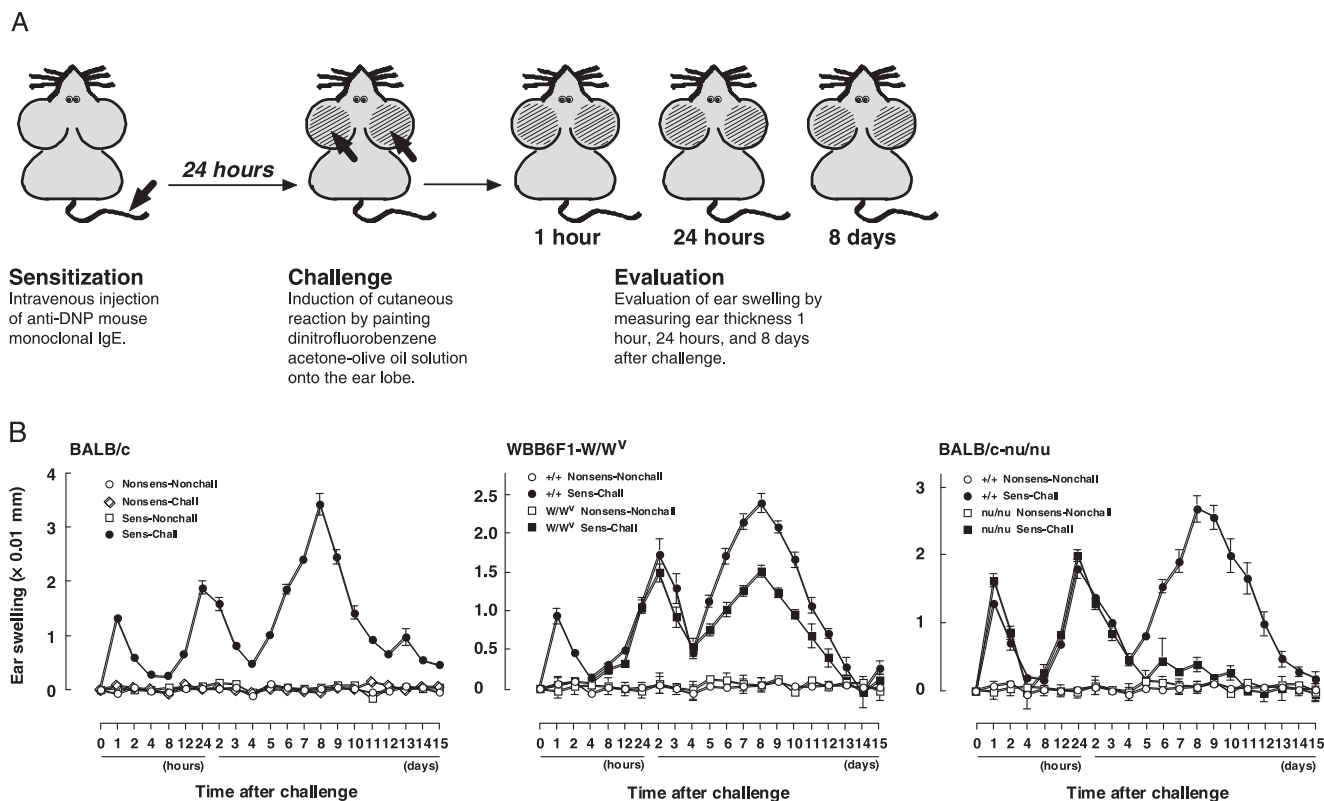


**Fig. 2.** Protocol for triphasic cutaneous reaction (TpCR) (A) and TpCR in BALB/c, WBB6F1-W/W<sup>v</sup>, and BALB/c-nu/nu mice (B).

### Triphasic cutaneous reaction in the mouse ear

Biphasic ear swelling is induced upon challenge with 2,4-dinitrofluorobenzene (DNFB) onto the ear of BALB/c mice passively sensitized with anti-dinitrophenyl (DNP) monoclonal IgE (12). Female BALB/c mice are passively and systemically sensitized by an intravenous injection of anti-DNP monoclonal IgE. Cutaneous reaction is evoked by painting with DNFB acetone-olive oil solution onto the ear lobe 48 h after the sensitization. Ear swelling appears biphasically with peak responses at 15–30 min and 24–48 h after challenge with DNFB. The swelling is IgE-dependent and the first phase response is mast cell-dependent. However, the second phase response is induced in mast cell-deficient WBB6F1-W/W<sup>v</sup> mice, suggesting that the response could be induced mast cell-independently. The DNFB-induced ear swelling in passively sensitized BALB/c mice was suggested to be useful as a model for human atopic dermatitis (13).

The first phase ear swelling is dependent on mast cells and inhibited by mast cell stabilizers and antihistamines (14). In contrast, inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-1 $\beta$  seem to participate in the second phase response (15, 16). TNF- $\alpha$

and IL-1 $\beta$  induce ear swelling similar to the second phase response, and antibodies against TNF- $\alpha$  and IL-1 $\beta$  clearly inhibit the second phase ear swelling. Glucocorticoids inhibit both phases of ear swelling potently.

In 1999, Tahara et al. found that a potent and persistent ear swelling is induced following the second phase response (17). Peak response of the third phase ear swelling is observed at 8 days after DNFB challenge and the swelling is characterized by intense eosinophil accumulation. The third phase ear swelling is reduced partially in mast cell-deficient WBB6F1-W/W<sup>v</sup> mice and almost completely disappears in BALB/c-nu/nu mice (17, 18). These results suggest that mast cells and T cells play important roles in the induction of the third phase response. Although anti-CD4 and anti-CD8 antibodies do not affect the first and second phase responses, anti-CD4 antibodies significantly potentiate, but anti-CD8 antibodies significantly inhibit the third phase response. Therefore, CD8<sup>+</sup> T cells seem to be important for the induction of the third phase response, but CD4<sup>+</sup> T cells may play regulatory roles. Although glucocorticoids inhibit all phases of ear swelling, cyclosporine A and tacrolimus only inhibit the third phase response.

Our protocol for the induction of triphasic cutaneous

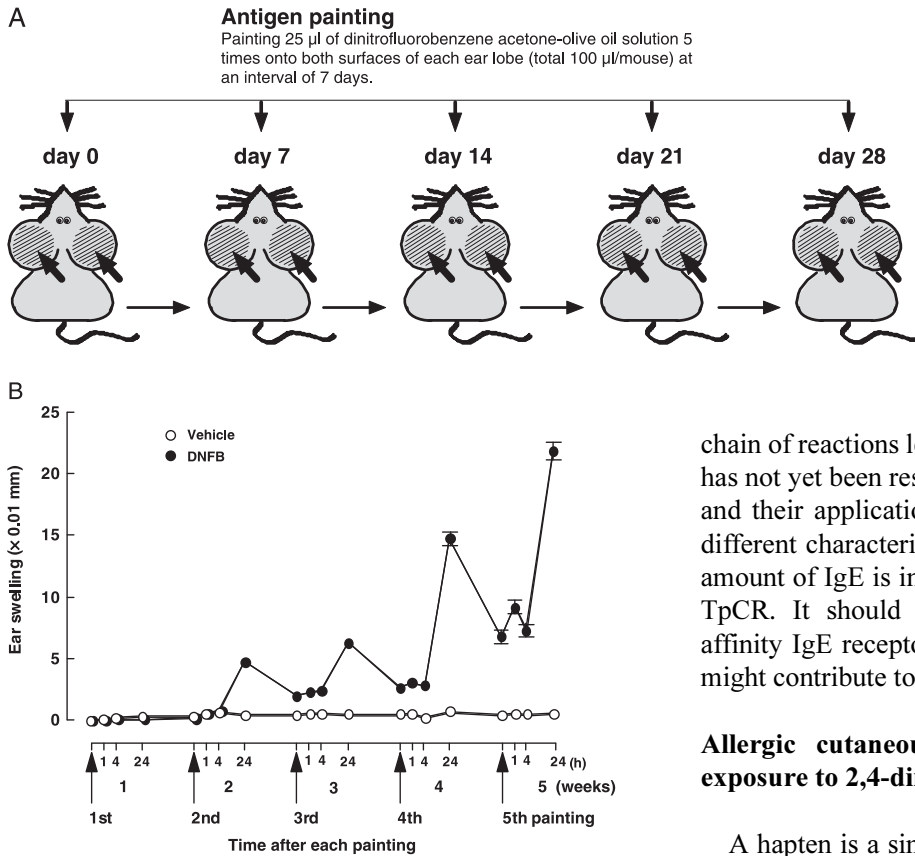


**Fig. 3.** Protocol for hapten-induced allergic dermatitis (A) and typical example in BALB/c mice (B).

reaction (TpCR) and typical examples are shown in Fig. 2. Under our experimental protocol, peak responses of the 3 phases appear 1 h, 24 h, and 8 days after the DNFB challenge. The time course of the ear swelling is highly reproducible in many strains of mice except for mast cell- and T cell-deficient mice.

Another TpCR model has been reported by Karasuyama and his colleagues (19, 20). BALB/c mice are passively sensitized by an intravenous injection of trinitrophenyl (TNP)-specific IgE 1 day before challenge by an injection of TNP-OVA into the ear lobe. The peak response for the third phase ear swelling appears 3 days after the challenge, and the swelling is characterized by massive eosinophil infiltration similar to the third phase caused by DNFB. In clear contrast to the case of the DNFB-induced response, however, the third phase response caused by TNP-OVA is dependent on neither mast cells nor T cells, and basophils are critical for the induction of the response. A small number of basophils triggers the response and some potentiating mechanisms are suggested.

As TpCR is a passively sensitized model, underlying mechanisms are expected to be simple. However, the

chain of reactions leading to the third phase ear swelling has not yet been resolved completely. Different antigens and their application routes may lead to a TpCR with different characteristics. Furthermore, a relatively large amount of IgE is injected for the sensitization to induce TpCR. It should be considered, therefore, that low affinity IgE receptors as well as high affinity receptors might contribute to the induction of TpCR.

#### Allergic cutaneous reaction caused by repeated exposure to 2,4-dinitrofluorobenzene

A hapten is a simple chemical that acts as an antigen but does not induce an immune response. Haptens reactive to proteins sometimes act as contact sensitizers to cause delayed-type cutaneous reaction. The reaction with a peak response at 24–48 h after stimulation is T cell-mediated, and CD4<sup>+</sup> T helper cell type 1 (Th1) is known to play important roles in the induction of delayed-type cutaneous reaction.

In 1995, Kitagaki et al. reported that repeated epicutaneous application of a contact sensitizing hapten, 2,4,6-trinitrochlorobenzene (TNCB), causes a shift from a delayed-type cutaneous reaction to an immediate-type response followed by a late reaction (21). Repeated TNCB application also causes epidermal hyperplasia, accumulation of large numbers of CD4<sup>+</sup> T cells and mast cells, and elevated serum levels of antigen-specific IgE. The immediate cutaneous response and IgE production are considered to be dependent on T helper cell type 2 (Th2). Furthermore, the repeated elicitation of the contact hypersensitivity reaction induces a shift in cutaneous cytokine milieu from a Th1 to a Th2 profile (22). The dermatitis caused by repeated epicutaneous application of a hapten may be a useful model for human atopic dermatitis.

We studied a dermatitis model caused by repeated application of another contact sensitizing hapten, 2,4-dinitrofluorobenzene (DNFB) (23, 24). DNFB acetone-olive oil solution is epicutaneously applied 5 times onto

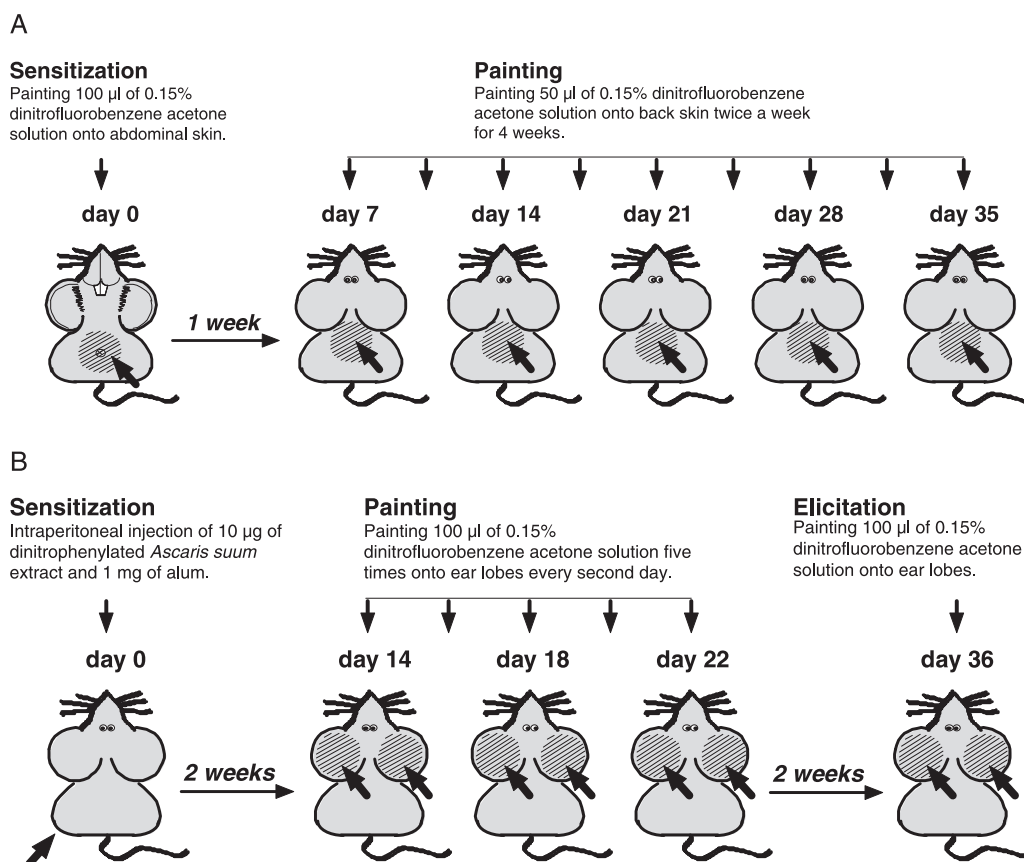


**Fig. 4.** Protocols for inducing allergic dermatitis in the back skin (A) and ear (B) associated with frequent scratching behavior by repeated exposure to hapten.

the ear of BALB/c mice at an interval of 7 days (Fig. 3A). Ear swelling caused by DNFB application increases in proportion to the number of applications, and eczematous changes of the skin is associated with marked infiltration of neutrophils, eosinophils and monocytes, and epidermal hypertrophy. Ear swelling reaches a maximum 24 h after the second, third, and fourth applications; and after the fifth application, the swelling becomes biphasic with peaks at 1 and 24 h (Fig. 3B). Repeated application of DNFB also causes the elevation of serum levels of antigen-specific IgE. Expression of germline and productive C $\epsilon$  mRNA can be detected in cervical lymph nodes, but only productive C $\epsilon$  mRNA is detectable in the spleen. However, Th2 cytokine mRNA expression in the lesion is hardly detectable under this experimental protocol.

To detect stable Th2 cytokine expression in the lesion, we modified the experimental protocol (Fig. 4). We examined 2 experimental protocols using clipped back skin and ear of BALB/c mice. In these protocols, as we aimed to observe scratching behavior at the same time, DNFB was dissolved in acetone, because olive oil may induce scratching behavior by itself. Back skin dermatitis

is induced by repeated application of DNFB-acetone solution 2 times a week for 4 weeks. Mice are sensitized previously with DNFB by painting the DNFB-acetone solution onto the abdominal skin 1 week before starting the repeated application (Fig. 4A). In the case of ear dermatitis, mice are immunized with dinitrophenylated *Ascaris suum* extract and aluminum hydroxide gel to induce IgE production. Two weeks after the immunization, DNFB-acetone solution is epicutaneously applied 5 times onto the ear every other day. Two weeks after the repeated application of DNFB, mice are finally challenged by painting with DNFB solution similarly (Fig. 4B). The dermatitis elicited in the ear can be evaluated by the swelling repeatedly.

The characteristics of the dermatitis caused under these protocols are similar. Repeated application of DNFB causes eczematous skin lesions associated with thickening of the epidermis and dermis, infiltration of inflammatory cells such as mast cells and eosinophils, potentiation of Th1 cytokine mRNA expression, and induction of Th2 cytokine mRNA expression. Elevated serum levels of antigen-specific IgE are also observed. Furthermore, upon application with DNFB, frequent

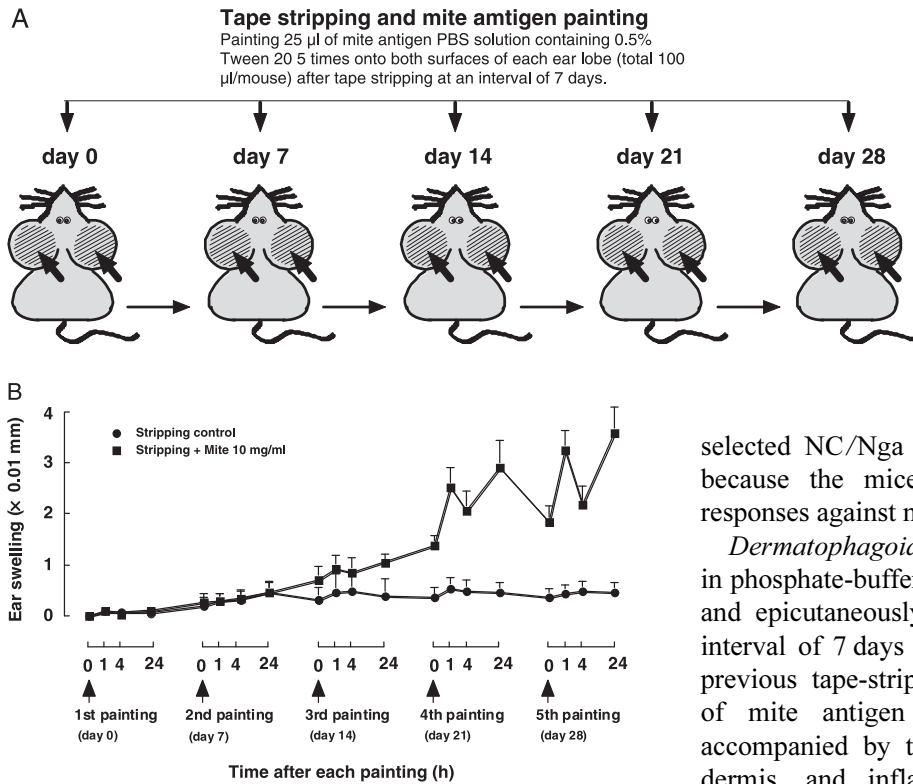


**Fig. 5.** Protocol for mite antigen-induced allergic dermatitis (A) and typical example in BALB/c mice (B.)

scratching behavior is induced. For the evaluation of scratching behavior, we established an apparatus, MicroAct, that detects consecutive scratching behavior consisting of 3 or more beats automatically (25). Dexamethasone exhibits potent inhibitory effect on the dermatitis. Dexamethasone inhibits interferon (IFN)- $\gamma$ , IL-4, and IL-5 mRNA expression and completely reduces eosinophil accumulation. However, the drug does not affect the induction of scratching behavior. In contrast, although the anti-inflammatory activity of tacrolimus is weaker than that of dexamethasone, it inhibits the induction of scratching behavior potently. We further demonstrated that tacrolimus inhibits the extension of nerve fibers into the epidermis (26). Inhibition of nerve fiber extension may contribute to the inhibition of scratching behavior by tacrolimus.

### Allergic cutaneous reaction caused by repeated exposure to mite antigen

House dust mite is an important indoor allergen and sometimes a cause for allergic rhinitis and bronchial asthma. As it is also an important allergen for the onset and/or development of atopic dermatitis, we attempted to induce an allergic dermatitis using mite antigen. We

selected NC/Nga (27) mice to induce the dermatitis because the mice seem to exhibit potent allergic responses against mite antigen.

*Dermatophagoides farinae* crude extract is dissolved in phosphate-buffered saline containing 0.5% Tween 20 and epicutaneously applied 5 times repeatedly at an interval of 7 days onto the ear of NC/Nga mice with previous tape-stripping (Fig. 5). Repeated application of mite antigen causes eczematous skin lesions accompanied by thickening of epidermis, fibrosis of dermis, and inflammatory cell accumulation (28). Apparent biphasic ear swelling is observed after the fourth and fifth applications. Elevation of serum IgE levels is also induced. It is interesting to note that application of mite antigen to NC/Nga mice induces decreased expression of IFN- $\gamma$  mRNA and increased expression of IL-4 mRNA in both lymph nodes and ears. Therefore, treatment of NC/Nga mice with mite antigen seem to skew the Th1/Th2 balance to Th2, and the dermatitis in NC/Nga mice seem to be useful for the basic study of atopic dermatitis.

Itching is one of the most important symptoms in atopic dermatitis. However, repeated epicutaneous application of mite antigen solution onto the ear of NC/Nga mice does not cause frequent scratching behavior. Development of a new mite antigen-induced allergic dermatitis model in NC/Nga mice with frequent scratching behavior is now underway.

### Naturally occurring allergic dermatitis models

NC/Nga mice established in the 1950s by Kondo develop a dermatitis spontaneously under a conventional condition (27). Apparent and severe eczematous skin lesions are induced that are associated with frequent scratching behavior and elevated levels of serum IgE. The frequent scratching behavior plays an important role to worsen and develop the skin lesion. At present, the naturally occurring dermatitis in NC/Nga mice seems to be the most frequently used model for the basic

study of atopic dermatitis. Although the dermatitis in NC/Nga mice could be induced by infestation with fur mites, the developmental mechanism of the dermatitis has not been elucidated. Therefore, it sometimes is difficult to control the development and severity of dermatitis.

NOA (Naruto Research Institute Otsuka Atrichia) mouse, a hair-deficient mutant, develops ulcerative skin lesions associated with a remarkable histology that features large numbers of mast cells and eosinophils in specific pathogen-free condition (29). Furthermore, the dermatitis in NOA mice is also associated with elevated levels of serum IgE and frequent scratching behavior. It is suggested that socio-psychological factors seem to be involved in the etiology of wet skin lesions.

DS-*Nh* mouse is a spontaneous hairless mutant of DS mouse and develops spontaneous dermatitis under specific pathogen-free condition (30). The dermatitis is associated with hyperproduction of serum IgE. *Staphylococcus aureus* infection seems to be associated with the dermatitis. Recently, a mutation in transient receptor potential cation channel V3 has been confirmed to be associated with hairlessness and development of dermatitis in DS-*Nh* mice.

Mutant model animals for human diseases are interesting and important for identifying causative genes for the diseases, although identification of the gene may be sometimes difficult.

### Spontaneous dermatitis in gene-knockout and transgenic mice

Recently, development of gene technology has made it possible to produce gene-altered mice easily, and many gene-knockout and transgenic mice have been developed. As shown in Table 1, many gene-knockout and transgenic mice developing atopic dermatitis-like symptoms spontaneously have been reported. Overexpression of Th2 cytokines (IL-4-, IL-13-, and BAC-transgenic mice) and thymic stromal lymphopoietin (TSLP-transgenic mouse) develop atopic dermatitis-like symptoms, suggesting that the Th2 response is important for the onset and/or development of atopic dermatitis. Shift from the Th1 response to the Th2 response and Th1/Th2 balance skewed to Th2 are observed in some models caused by repeated exposure to antigens as mentioned above. Interestingly, RelB-knockout mice develop atopic dermatitis-like symptoms spontaneously, although it is a member of the nuclear factor (NF)- $\kappa$ B/Rel family of transcription factors. The NF- $\kappa$ B/Rel family members influence helper T cell differentiation, and RelB is expressed predominantly in Th1 cells. Disruption of an inhibitor of  $\kappa$ B (I $\kappa$ B) protein, I $\kappa$ B $\zeta$ ,

is also reported to lead to severe atopic dermatitis-like disease. NF- $\kappa$ B is a well known transcription factor that facilitates cytokine expression responsible for allergic inflammation. RelB-knockout mice developing atopic dermatitis-like disease as well as autoimmune diseases may show a new aspect of the transcription factor. Furthermore, importance of IL-18 has been indicated by IL-18-transgenic mice, caspase 1-transgenic mice, and cathepsin E-knockout mice. Cathepsin E-knockout mice develop atopic dermatitis-like symptoms under a conventional condition similar to the case of NC/Nga mice.

Development of atopic dermatitis is considered to be dependent on both genetic and environmental factors. Although many genes have been proposed as causative ones for the disease, it is sometimes difficult to confirm what these genes are in patients. Therefore, gene-altered mice developing atopic dermatitis-like diseases are very useful tools to confirm the role of the gene products in the onset and/or development of the disease. Furthermore, newly generated gene-altered mice may allow us to identify new molecules important for the disease. Roles of Th2-skewed responses in atopic dermatitis patients seem to be well supported by some gene-altered mice.

### Conclusion

Animal models for human diseases are useful and important for elucidating the mechanisms involved in these diseases as well as for the establishment of effective treatment strategies for them. Many animal models for allergic dermatitis with distinct characteristics have been proposed. Usually an animal model for human diseases reflects only some aspects of the disease. Therefore, we should consider the characteristics of each model and employ several models comparatively.

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