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The Transfer of Maternal Antigen-specific IgG Regulates the Development
of Allergic Airway Inflammation Early in Life in the FcRn-dependent
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Running Title: The role of FcRn in allergic airway inflammation

Key words: allergic airway inflammation, asthma, IgG, FcRn, breast milk

Abstract

Asthma is the chronic inflammatory airway disease characterized by airway hyperreactivity, increased mucus production, and reversible airway contraction. Asthma is a complex genetic trait caused by environmental factors in genetically predisposed individuals. The transportation of maternal antigen specific IgG via amniotic fluid, placenta and breast milk plays an important role in the passive immunity. First, in order to examine whether maternal passive immunity by the transportation of antigen specific IgG via FcRn regulates allergic airway inflammation, ovalbumin-immunized FcRn^{+/+} female mice were bred with FcRn^{-/-} male mice to evaluate the degree of ovalbumin-induced allergic airway inflammation of FcRn^{-/-} offspring. Maternal passive immunity regulated allergic airway inflammation in the FcRn-dependent manner. Second, in order to examine the role of maternal antigen specific IgG1 injection into mothers, ovalbumin-specific IgG1 was injected intravenously into wild-type or FcRn^{+/+} mother immediately after birth. Offspring were sensitized and challenged with ovalbumin. Antigen specific IgG1 administered into mother mice during lactating period reduced allergic airway inflammation of offspring in the FcRn-dependent manner. Last, in order to exclude the factor of maternal passive immunity except

ovalbumin-specific IgG1, we administered ovalbumin-specific IgG1 orally to offspring after birth. Oral administration of ovalbumin-specific IgG1 to offspring during lactating period prevented the development of an allergic airway inflammation in the FcRn-dependent manner. These data show the transfer of maternal antigen-specific IgG regulates the development of allergic airway inflammation early in life in the FcRn-dependent manner.

Introduction

Asthma is the chronic inflammatory airway disease characterized by airway hyperreactivity, increased mucus production, and reversible airway contraction. Lymphocytes, mast cells, eosinophils, and basophils infiltrate the airway of asthma patient. Chemical mediators and cytokines secreted from these cells form chronic airway inflammation. Especially, Th2 cytokines such as interleukin 4 (IL-4), IL-5, IL-13 are important for airway inflammation (1).

In recent years, the prevalence of asthma is increasing in both adults and children (2). Asthma is a complex genetic trait caused by environmental factors in genetically predisposed individuals (1). It is reported that atopic asthma is a hereditary disease because it develops from the infancy (3). There are some reports that the development of allergic disease such as

asthma, atopic dermatitis, and atopic conjunctivitis during the adolescent period is reduced in the children from the mother sensitized with allergens before or during pregnancy and lactation (4-9). Transportation of Th-2 cell (7), IFN- γ (8) or antigen specific IgG from mother to offspring reduce the development of allergic diseases. Especially, the transportation of maternal antigen specific IgG via amniotic fluid, placenta and breast milk plays an important role in the passive immunity (7-9). The neonatal Fc receptor for IgG (FcRn) has been well characterized in the transfer of passive humoral immunity from mother to her fetus. Therefore FcRn that expresses on placenta, intestinal epithelia, liver, lung, and vascular endothelium plays the important role in the transportation of maternal IgG (10).

FcRn binds to the Fc domain of IgG at acidic pH ($\text{pH} < 6.0$) but not at a physiological pH ($\text{pH} > 7.0$) (11) and functions in the bidirectional transport of IgG across polarized epithelia (12) and a related cell biologic process that is associated with the protection of monomeric IgG from degradation (13). FcRn also regulates mucosal immune responses to luminal bacteria and pathogenesis of colitis(14,15).

First, we confirmed that the development of the allergic airway inflammation is reduced in the FcRn-dependent manner by sensitizing mother mice before pregnancy and inducing allergy. Next, we evaluated the

effect of the antigen specific IgG in the breast milk whether it can reduce the development of allergic airway inflammation of offspring. Offspring were sensitized and challenged with ovalbumin.

Materials and Methods

Animals

Six- to eight-week-old female C57BL/6 mice (WT; specific pathogen free, Nippon CLEA, Tokyo, Japan) and FcRn^{+/-}, FcRn^{-/-} mice (16) weighing 22 to 25 g were prepared. All animal experiments were undertaken according to the Guidelines for Animal Experimentation at Kobe University Graduate School of Medicine. Our research was approved by the Institutional Animal Care and Use Committee and carried out according to the Kobe University Animal Experimentation Regulations.

Agents

The following drugs and chemicals were purchased commercially: ovalbumin (OVA; Sigma-Aldrich Japan, Tokyo, Japan). Mouse OVA specific IgG1 was kindly gifted from H.Karasuyama (Department of Immune Regulation, Tokyo Medical and Dental University Graduate

School.).

Sensitization and antigen challenge.

Six-to eight-week-old female WT, FcRn^{+/-}, FcRn^{-/-} mice were sensitized with intraperitoneal injections of 50µg of OVA with 1mg of alum twice or three times. Then, they were exposed to 1% (wt/vol) OVA diluted in sterile phosphate-buffered saline (PBS) for 30 min on 3 consecutive days.

Collection of bronchoalveolar lavage fluid

Twenty-four hours after last exposure, bronchoalveolar lavage (BAL) was performed by instilling and aspirating two 0.8-ml aliquots of PBS (recovery >85%). Cells in the lavage fluid were counted by using a hemocytometer. BAL fluid was centrifuged at 1500 g for 5 min (at 4°C).

Lung histology

Mouse lungs were intratracheally instilled with 10% buffered formalin at a pressure of 20cmH₂O for 24h and then embedded in paraffin. They were stained with hematoxylin and eosin or with periodic acid-Schiff.

Collection of blood

Blood was collected from heart via the anterior mediastinum. Blood was centrifuged at 3000 g for 10 min (at 4°C), and supernatants were stored at -20°C.

Immunoglobulin assay

Mouse OVA-specific IgG1 serum levels were measured by using a MOUSE IgG1 ELISA KIT (BETHYL). Mouse OVA-specific IgE serum levels were measured by using a DS Mouse IgE ELISA (DS Pharma Biomedical Co.,Ltd.)

Statistical analysis

Results are expressed as means \pm SE. Statistical significance between groups was assessed by Mann Whitney test. The p values for significance were set at 0.05.

Results

FcRn^{-/-} mice has the same of susceptibility in allergic airway inflammation as wild-type mice .

FcRn plays an important role in the transportation of maternal antigen specific IgG (10). However it is not known that what kind of influence on allergic airway inflammation FcRn has. First, we evaluated the degree of allergic airway inflammation of wild-type mice, FcRn^{+/-} mice, and FcRn^{-/-} mice. 6 to 8 weeks old mice were sensitized on day 0, 7, 14, and challenged with OVA on day 21-23 respectively. The effects of FcRn in airway inflammation were assessed by cell counts of BALF and histological analysis on day 24 (Figure 1A). There were no significant difference in the counts of total cells and eosinophils in the BALF and in the airway inflammation and mucus production among WT, FcRn^{+/-} and FcRn^{-/-} mice (Figure 1B, C). These results indicated that FcRn^{+/-} and FcRn^{-/-} mice have the same of susceptibility in allergic airway inflammation as wild type mice.

Maternal passive immunity can regulate allergic airway inflammation in the FcRn-dependent manner.

In order to examine whether maternal passive immunity by the transportation of antigen specific IgG via FcRn regulates allergic airway inflammation, OVA-immunized FcRn^{+/-} female mice were bred with FcRn^{-/-} male mice to evaluate OVA-induced allergic airway inflammation of FcRn^{-/-} offspring.

Wild-type and FcRn^{+/-} female mice were immunized with OVA and alum before pregnancy on day 0, 14, 21, and challenged with nebulized OVA during pregnancy respectively. They were bred with wild-type and FcRn^{-/-} male mice respectively. Offspring were sensitized with OVA and alum on day 28 and 35. Serum OVA-specific IgE levels were analyzed in offspring on day 42, and challenged with nebulized OVA on day 43-45. Airway inflammation were assessed by cell counts of BALF on day 46 (Figure 2A). By sensitizing mother before pregnancy and inducing allergic airway inflammation during pregnancy, serum OVA-specific IgE level was significantly reduced in wild-type offspring, but not in FcRn^{-/-} offspring (WT offspring from immunized mother, 8.676 ± 3.841 ng / ml; FcRn^{-/-} offspring, 83.40 ± 28.67 ng / ml; WT offspring from naïve mother, 84.32 ± 23.84 ng / ml; $p < 0.05$; Figure 2B). The cell counts of BALF were significantly reduced in wild-type offspring from immunized mother, but FcRn^{-/-} offspring were not (WT offspring from immunized mother, total

cells; $14.0 \pm 8.04 \times 10^4 / l$, eosinophils; $3.84 \pm 3.93 \times 10^4 / \mu l$; FcRn^{-/-} offspring, total cells; $86.5 \pm 23.9 \times 10^4 / ml$, eosinophils; $65.9 \pm 22.9 \times 10^4 / ml$; WT offspring from naïve mother, total cells; $57.0 \pm 12.6 \times 10^4 / ml$, eosinophils; $36.7 \pm 14.4 \times 10^4 / ml$; $p < 0.05$; Figure 2C). These results indicated that maternal passive immunity regulates allergic airway inflammation in the FcRn-dependent manner.

The administration of antigen specific IgG1 into mother mice during lactating period can reduce allergic airway inflammation of their offspring in the FcRn-dependent manner.

In order to examine the role of maternal antigen specific IgG1 injection into mothers, OVA-specific IgG1 (1mg / body) was injected intravenously into wild-type or FcRn^{+/-} mother, immediately after birth (day 1). Offspring were sensitized with OVA and alum on day 28 and 35. Serum OVA-specific IgE levels were analyzed by ELISA on day 42, and challenged with nebulized OVA on day 43-45 respectively. Airway inflammation were assessed by cell counts of BALF on day 46 (Figure 3A). By intravenous administration of OVA-specific IgG1 to mother, OVA-specific IgE level was significantly reduced in wild-type offspring, but not in FcRn^{-/-} offspring (WT offspring from treated mother, 1.590 ± 1.171 ng / ml; FcRn^{-/-}

offspring, 75.66 ± 14.60 ng / ml; WT offspring from naïve mother, 58.65 ± 10.44 ng / ml; $p < 0.01$; Figure 3B). The cell counts of BALF were also significantly reduced in wild-type offspring from treated mother, but FcRn^{-/-} offspring were not (WT offspring from treated mother, total cells; $12.0 \pm 8.42 \times 10^4$ / ml, eosinophils; $2.23 \pm 2.76 \times 10^4$ / ml ; FcRn^{-/-} offspring, total cells; $85.3 \pm 25.1 \times 10^4$ / ml, eosinophils; $67.2 \pm 24.0 \times 10^4$ / ml; WT offspring from naïve mother, total cells; $57.0 \pm 12.6 \times 10^4$ / ml, eosinophils; $36.7 \pm 14.4 \times 10^4$ / ml ; $p < 0.05$; Figure 3C). By the way, OVA-specific IgG1 levels of breast milk was not significantly different between wild-type mother and FcRn^{+/-} mother (WT mother, 1.59 ± 0.60 ng / ml; FcRn^{+/-} mother, 1.27 ± 0.77 ng / ml). These results indicated that antigen specific IgG1 administered into mother mice during lactating period was secreted into breast milk, and it reduced allergic airway inflammation of their offspring in the FcRn-dependent manner.

Oral administration of OVA-specific IgG1 into offspring during lactating period can prevent the development of an allergic airway inflammation in the FcRn-dependent manner.

In order to exclude the factor of maternal passive immunity except OVA specific IgG1, we administered OVA specific IgG1 ($10\mu\text{g}$ / ml) orally to

offspring according to the following schedule. Serum OVA specific IgG1 levels of offspring were analyzed on day 19. Wild-type and FcRn^{-/-} offspring were sensitized with OVA and alum on day 28 and 35. OVA specific IgE levels were analyzed on day 42. Then they were challenged with nebulized OVA on day 43-45. Airway inflammation were assessed by cell counts of BALF and histological analysis on day 46 (Figure 4A). By oral administration of OVA-specific IgG1 to offspring, serum OVA-specific IgG1 level in offspring was significantly reduced in FcRn^{-/-} (treated WT, 71.18 ± 14.62 ng / ml; treated FcRn^{-/-} 14.00 ± 0.258 ng / ml; $p < 0.01$; Figure 4B). OVA specific IgE level was significantly reduced in wild type offspring, but not in FcRn^{-/-} offspring (treated WT offspring, 12.49 ± 3.79 ng / ml; FcRn^{-/-} offspring, 64.70 ± 28.54 ng / ml; WT offspring from naïve mother, 58.65 ± 10.44 ng / ml; $p < 0.05$; Figure 4C). Airway inflammation was also significantly inhibited in treated wild-type offspring, but not in FcRn^{-/-} offspring (treated WT, total cells; $21.0 \pm 12.7 \times 10^4$ / ml, eosinophils; $13.8 \pm 21.8 \times 10^4$ / ml; FcRn^{-/-} offspring, total cells; $70.6 \pm 29.7 \times 10^4$ / ml, eosinophils; $54.9 \pm 28.7 \times 10^4$ / ml; untreated WT, total cells; $57.0 \pm 12.6 \times 10^4$ / ml, eosinophils; $36.7 \pm 14.4 \times 10^4$ / ml; $p < 0.05$; Figure 4D). Histological analysis of hematoxylin and eosin or periodic acid-Schiff stained lung sections isolated from the treated wild-type

offspring showed less inflammatory infiltrates and mucus production in the airways compared with the FcRn^{-/-} offspring or wild-type offspring of naïve mother (Figure 4E). These results indicated that oral administration of OVA-specific IgG1 to offspring during lactating period can prevent the development of an allergic airway inflammation in the FcRn-dependent manner.

Discussion

It is not known that what kind of influence on allergic airway inflammation FcRn has. We confirmed that the development of the allergic airway inflammation was reduced in the FcRn-dependent manner by sensitizing mother mice before pregnancy and inducing allergy. The degree of allergic airway inflammation of FcRn^{-/-} mice was comparable with that of wild-type mice (Figure 1B). It thinks that, FcRn itself does not affect the development of the allergic airway inflammation by OVA because FcRn expresses only in mouse alveolar epithelial cells very low levels but not in airway epithelial cells (17).

There are some reports that maternal passive immunity suppresses the development of allergic disease during the adolescent period (4-9). The transportation of maternal antigen specific IgG via amniotic fluid, placenta

and breast milk plays an important role in the passive immunity (7-9). FcRn plays an important role in the transportation of maternal antigen specific IgG (10). So FcRn must have suppressive role on passive immunity. First, we confirmed that maternal passive immunity on allergic airway inflammation can be reduced in the FcRn-dependent manner (Figure 2B, C). Different from our study, T.Polte reported that, maternal tolerance were observed only when both of the wild type and FcRn^{-/-} offspring were nursed by their own mothers and not when nursed by naïve wet-nurses (8). It was explained that breastfeeding was crucial for maternal passive immunity because OVA specific IgG1 was not transported from mother to offspring in FcRn^{-/-} mice via placenta. T.Polte also reported that serum OVA specific IgG1 level was increased in wild type fetus. However FcRn doesn't express in placenta in rodents (10). H.Uthoff reported that OVA were transported from mother to their fetus by amniotic fluid or placenta when mother mice were exposed by OVA during pregnancy (7). That is why increase of the serum OVA-specific IgG1 level in wild-type fetus might explain by the exposure of OVA in the fetal-period. Exposure of OVA during fetal-period might also affect the reduction of allergic airway inflammation of FcRn^{-/-} offspring.

In order to exclude the influence of OVA exposed during fetal-period, we

injected OVA-specific IgG1 intravenously to puerperant wild-type and FcRn^{+/-} mother immediately after delivery. OVA-specific IgG1 level of the breast milk from FcRn^{+/-} mother was in the same range of those from wild-type mother. We confirmed that antigen specific IgG1 injected into mother mice during lactation period was secreted into breast milk, and it reduced allergic airway inflammation of their offspring in the FcRn-dependent manner (Figure3 B,C).

In order to exclude the factor of maternal passive immunity except OVA-specific IgG1, we administered OVA-specific IgG1 orally to offspring. We confirmed that oral administration of OVA-specific IgG1 to offspring during lactating period can prevent the development of an allergic airway inflammation in the FcRn-dependent manner. By oral administration of OVA-specific IgG1 to offspring, serum OVA-specific IgG1 level in offspring was significantly reduced in FcRn^{-/-} offspring. The uptake of OVA-specific IgG1 in the breast milk via FcRn expressing on the epithelial cell of intestine must important for the transportation of OVA-specific IgG1 from mother to offspring.

Previous studies showed that the transportation of IFN- γ (8) or Th-2 cell (7) with OVA specific IgG is necessary for maternal passive immunity. Our study showed that maternal OVA specific IgG1 in breast milk transported

via FcRn in the epithelial-cell layer of intestine alone can prevent the development of allergic airway inflammation of OVA during young days.

Conclusion

In this study, we confirmed that the immune therapy before or during pregnancy and lactating period is beneficial to reduce the development of allergic disease during young days. It is necessary to pay attention to antigen exposure and immune therapy before conception, during pregnancy or breast feeding period in order to prevent allergy.

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Figure Legends

Figure 1

FcRn^{-/-} mice has the same of susceptibility in allergic airway inflammation as wild type mice.

- A. 6 to 8 weeks old C57BL/6 (WT), FcRn^{+/-} and FcRn^{-/-} mice were sensitized on day 0, 7, 14, and challenged with nebulized OVA on day 21-23. The effects of FcRn on airway inflammation were assessed by cell counts of BALF on day 24.
- B. There were no significant difference in the counts of total cells and eosinophils in the BALF between WT, FcRn^{+/-} and FcRn^{-/-} mice.
- C. There were no significant difference in the inflammation and mucus production between WT, FcRn^{+/-} and FcRn^{-/-} mice.

Figure 2

Maternal passive immunity can regulate allergic airway inflammation in the FcRn-dependent manner.

- A. Wild type and FcRn^{+/-} female mice were immunized with OVA and alum before pregnancy on day 0, 14, 21, and challenged with nebulized OVA during pregnancy respectively. They were bred with wild type and

FcRn^{-/-} male mice respectively. Offspring were sensitized with OVA and alum on day 28 and 35. Serum OVA specific IgE levels were analyzed in offspring on day 42, and challenged with nebulized OVA on day 43-45. Airway inflammation were assessed by cell counts of BALF on day 46.

- B. By sensitizing mother, serum OVA specific IgE level was significantly reduced in WT offspring, but not in FcRn^{-/-} offspring.
- C. The cell counts of BALF were significantly reduced in WT offspring from immunized mother, but FcRn^{-/-} offspring were not. Data are expressed as means \pm SE. *p < 0.05 vs. WT treated, Mann Whitney test.

Figure 3

The administration of antigen specific IgG1 into mother mice during lactating period can reduce allergic airway inflammation of their offspring in the FcRn-dependent manner.

- A. OVA-specific IgG1 (1mg / body) was injected intravenously into wild type or FcRn^{+/-} mother, immediately after birth (day 1). Offspring were sensitized with OVA and alum on day 28 and 35. Serum OVA specific IgE levels were analyzed by ELISA on day 42, and challenged with nebulized OVA on day 43-45 respectively. Airway inflammation were

assessed by cell counts of BALF on day 46.

- B. By intravenous administration of OVA-specific IgG1 to mother, OVA specific IgE level was significantly reduced in WT offspring, but not in FcRn^{-/-} offspring.
- C. The cell counts of BALF were significantly reduced in WT offspring from treated mother, but FcRn^{-/-} offspring were not. Data are expressed as means \pm SE. * $p < 0.05$ vs. WT treated, Mann Whitney test.

Figure 4

Oral administration of OVA-specific IgG1 into offspring during lactating period can prevent the development of an allergic airway inflammation in the FcRn-dependent manner.

- A. Serum OVA specific IgG1 levels of offspring were analyzed on day 19. Wild type and FcRn^{-/-} offspring were sensitized with OVA and alum on day 28 and 35. OVA specific IgE levels were analyzed on day 42. Then they were challenged with nebulized OVA on day 43-45. Airway inflammation were assessed by cell counts of BALF and histological analysis on day 46.
- B. Serum OVA-specific IgG1 level in offspring was significantly reduced in FcRn^{-/-}.

- C. By oral administration of OVA-specific IgG1 to offspring, OVA specific IgE level was significantly reduced in WT offspring, but not in FcRn^{-/-} offspring.
- D. The cell counts of BALF were significantly reduced in treated WT offspring, but not in FcRn^{-/-} offspring. Data are expressed as means \pm SE.
* $p < 0.05$ vs. WT treated, # $p < 0.01$, Mann Whitney test.
- E. Airway inflammation (hematoxylin and eosin) and mucus production (PAS) were significantly reduced in treated WT offspring, but not in FcRn^{-/-} offspring.

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Figure 1.

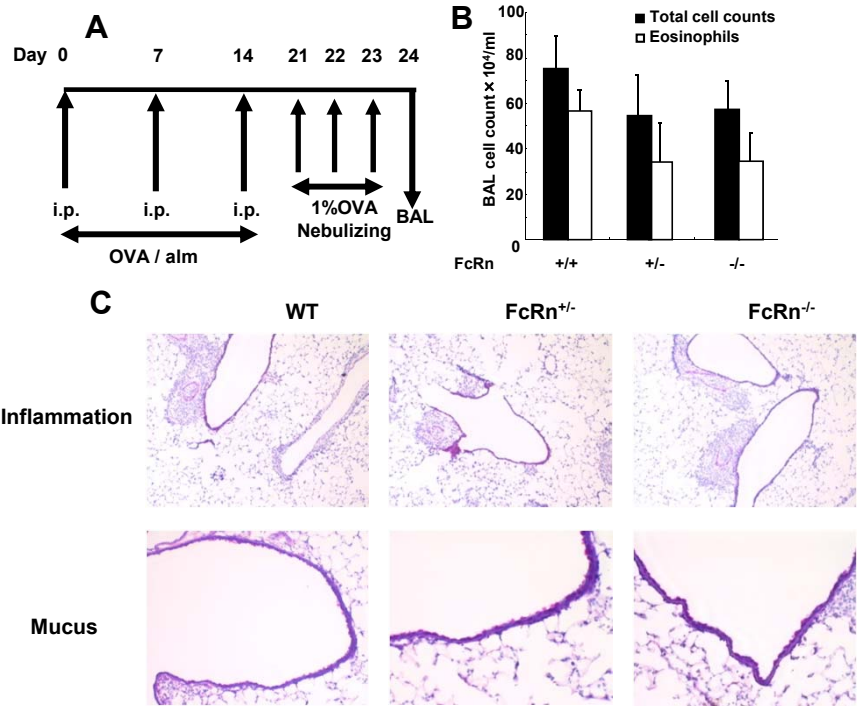


Figure 2.

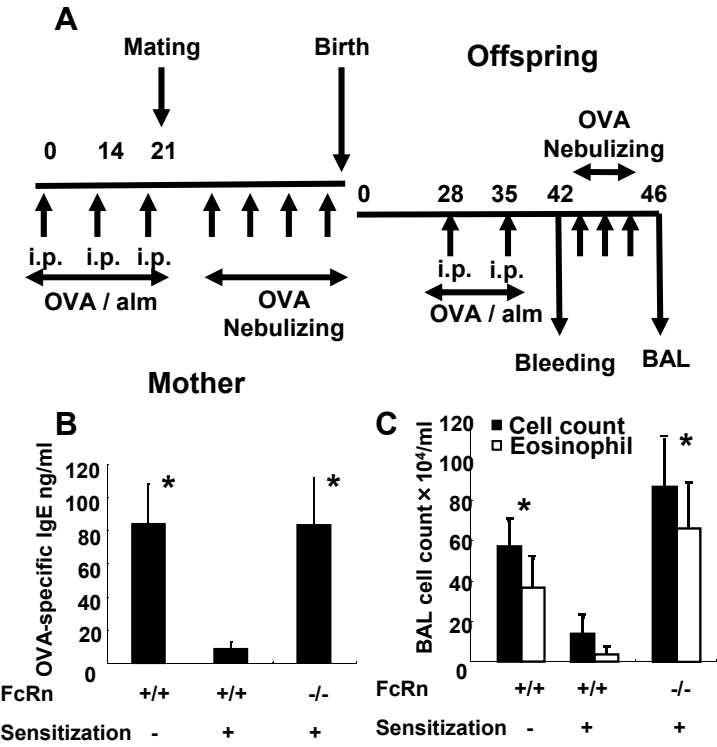


Figure 3.

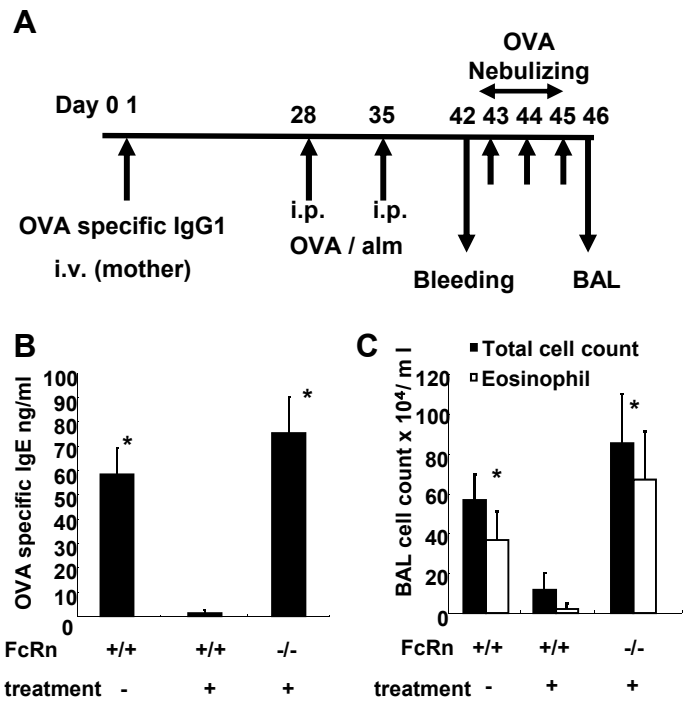


Figure 4.

