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Review Article

Maternal Lymphocyte Might Act as an Inductive Triggered Cell in Her Young as in Case of Atopic Allergy

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Abstract

An allergic responses including atopic allergy increased along with developed country where public health system were highly developed. The listed allergens were many as with botanical pollens and animal pest in surroundings. The purpose of this report was formulated to clarify a materno-fetal relation to the immune mechanism during pregnancy for sorting out to the atopic allergy. The test system were mainly designed for the inbred mouse in order to rule out first for the genetic background in mother and her young. We set up the series of experiment to confirm materno-fetal relation by biological aspect of pregnant mice especially in active immune responsiveness in mother mice and her young. The dosage and timing effect, the maternal active immune response was critical for her young. From backcross experiment in syngeneic strain of mice, maternal lymphoid cell trafficking was evident and biased to her offspring. The critical finding of effective span, 1/6 rodent life, suggests that the atopic allergy syndrome was close feature of rodent and human. From these finding, for prevent atopic allergy in children, maternal treatment might suggest to effective in order not develop atopic allergy to the same allergen. Even in some difficulties, we could expect that this maternal bias gave some light to her young avoiding atopic allergy.

Keywords: *Pregnancy; Materno-Fetal Relation; Maternal Bias; Active Immune Modulation; Specific T-Cell; MHC Restricted Cell Cooperation; Lymphocyte Trafficking to Young; Microchimerism; Atopic Allergy*

Abbreviation

APC: Antigen Presenting Cell; PEC: Peritoneal Exudate Cell; PFC: Plaque Forming Cell/Antibody Secreting Cell/Detection for Self-Productive of Antibody; MHC: Major Histocompatibility Complex; SPF: Specific Pathogens Free/Rearing System for Inbreed Animal; SRBC: Sheep Red Blood Cell/Good Antigen for Induce and Detect PFC; T_{off}: T Cell Prepared from Offspring Mice

Introduction

What is a biological significance of materno-fetal relation as an immunological stand point of view? Paternal genetic products is a foreign material of MHC to the better half/mother. In order to understand immunological back ground in human atopic allergy system [1-4], we tried to simplify first the genetic background in mother and her young. For this purpose, we select syngeneic strain of mice for this issue. We happen to find an immunological bias of mother to her young during pregnancy. When mother mice was immunized during pregnancy, her young was completely biased to active responsiveness in her baby [5-8]. This issue were continued until 1/6 of whole life of rodents, coinciding duration of the atopic alley syndrome in human [9-11]. Further analysis for immunological aspect, the key factor for the bias was depend on mother lymphocyte expressing CD4 lymphoid cell [12-15]. In heterogeneous relation between mother to her

young, this issue was also confirmed in her young, suggesting heterogeneous relation was expected rather serious than homogenous one. For mother mice can find heterogenic product in her baby where paternal gene product found in her baby. A natural immunity and acquired immunity are primary defense system of vertebrate animals. Despite the defense system built by these two types of immunity prevent our body from the invasion of external pathogens, improper immune response could develop allergic response, including atopic allergy [1-4].

Materno-fetal relation during pregnancy about active immune responsiveness in her young

In order to understand materno-fetal relation in pregnancy, we set up first setting up pregnant mice with pure strain of mice system. Pregnant C_3H/He mice were immunized with SRBC (5×10^8/head) intraperitoneally, 14 days of pregnant stage. In this immunizing condition, the mother developed good immune responses to SRBC.

The baby mouse was rearing to young adult, more than 6 weeks old.

The young adult mice were injected 5×10^8 of the same antigen SRBC. In that mice whose mother was immunized in pregnancy had suppressed their active immune response, cannot developed antibody secreting cell: PFC [16-18]. About humoral specific antibody on the other hand, an enough amount of anti-SRBC was passively transferred and found in the young serum [19,20]. The young mice who was delivered from mother immunized less than 107 SRBC, could respond further SRBC stimulation. This result indicated that the active immune response in mother was critical for induce active immune suppression in her young [21-24].

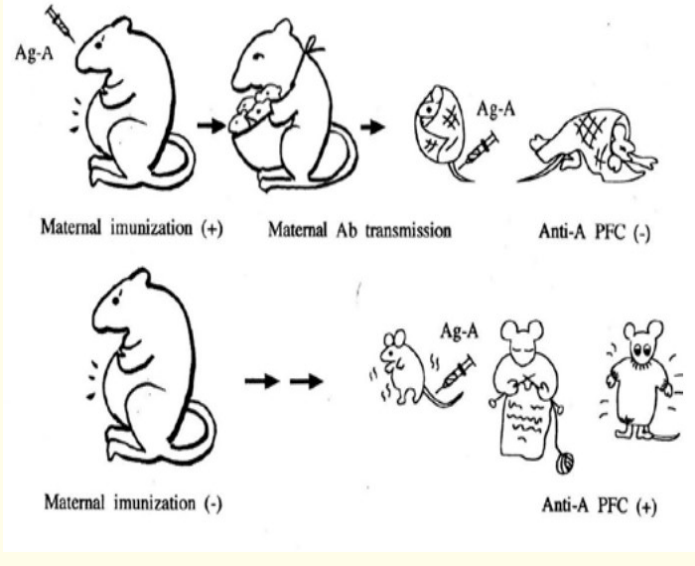

Figure 1: *Experimental Protocol: Effect of Maternal antigenic stimulation on the active immune responses in her offspring for experimental system.*

Mother mice were divided into two, control and experimental group. The experimental group received only saline. The young mice of both group were brought up to 6-8 weeks and then immunized with optimal amount, of corresponding antigens. The active antibody production was then detected by elegant method so-called plaque forming cell (PFC). After the antigenic stimulation, the experimental group of young did not respond and produce corresponding antibody, but the control group produce antibody forming cell that secrete specific antibodies.

Critical timing of gestation stage

So as to avoid the possibility of antigen transfer from mother to her embryo for this suppression, various stage of pregnant mouse were prepared and the active immune response was tested to the each offspring. The mother mice were prepared from five days before fertilization to three days before delivery [25]. In order to clarify the gestation stage for this bias, the mother was injected intraperitoneally SRBC antigen from -5days to 3 days before delivery. From this experiment, more than 5 days before pregnancy and after delivery did not induce maternal bias to her baby. These results indicated that induction phase of antibody response were critical for induce the bias in her young [25].

Stage of Gestation	% of Suppression in Young
-5 days	5 ± 7
0 days	8 ± 12
5 days	98 ± 7
10 days	95 ± 13
20 days	7 ± 9

Table 1: *Effective Timing of Immunization for Maternal Bias.*

The mothers were administered optimal amount of antigen/SRBC and all her offspring were immunized with optimal amount of SRBC antigen. After this trial, both groups that were immunolized five days before fertilization and five days before delivery did not induce suppression in offspring. These results indicated that induction phase of antibody response were critical for induce the bias in her young.

For understand this maternal bias more, the dosage experiment were planning for. A various dosages of SRBC were prepared and delivered from 10^5~10^9 of SRBC to a pregnant mice. The mother group who were administered an enough dosage were necessary for SRBC that induce active antibody production. Combined with pregnant stage and dosage experiment, maternal active immune response was critical for induce immunological bias in her young.

Antigen/SRBC	PFC Response (%)	
	Mother	Young
1 X 10^5	8 ± 9	103 ± 12
1 X 10^6	6 ± 11	98 ± 15
1 X 10^7	34 ± 16	45 ± 21
1 X 10^8	103 ± 12	7 ± 18
1 X 10^9	97 ± 16	5 ± 10

Table 2: *Effective Dosage of Antigen to Mother for this Bias.*

A various dosage of SRBC were prepared and delivered from 10^5~10^9 of SRBC to the pregnant mice. The mother group who were administered an enough dosage of SRBC that induce active antibody production. Combined with pregnant stage, maternal active immune response was critical for induce immunological bias in her young.

Active bias was good for 1/6 of life span

More to understand for the relationship between rodents and human as in case of atopic allergy, an experiment were designed for how long this bias was effective? The 10 group of mice were set up and followed the maternal bias. From this experiment, the maternal bias was confirmed until 20th week after delivery. This meant 1/6 of rodent life span was good for this bias [26]. This length corresponds

13 years old in human, coinciding the syndrome duration for age factor in human atopic allergy. The former experiment showed that the development of specific PFC could only be suppressed in offspring whose mothers were stimulated with an enough amount of SRBC. The data suggested that maternal transmitted antibodies were relevant for this bias. To test this possibility, pregnant mice were injected with a specific antiserum via the tail vein once or several times during gestation. These antiserum was collected from the same strain of mice which was immunized with 5×10^8 SRBC twice at an interval of 3 weeks. The titer of anti-SRBC IgG level was as high as 1:1024. The control group was injected with a normal serum from the same strain of mice. The offspring were kept in an environment, free from SPF for 6 weeks after delivery. The offspring from mice injected with the antiserum during pregnancy showed only a slight suppression that was almost the same as that of the offspring from the positive control group [27-29]. This trial suggest that the specific IgG antibody did not relevant for this bias.

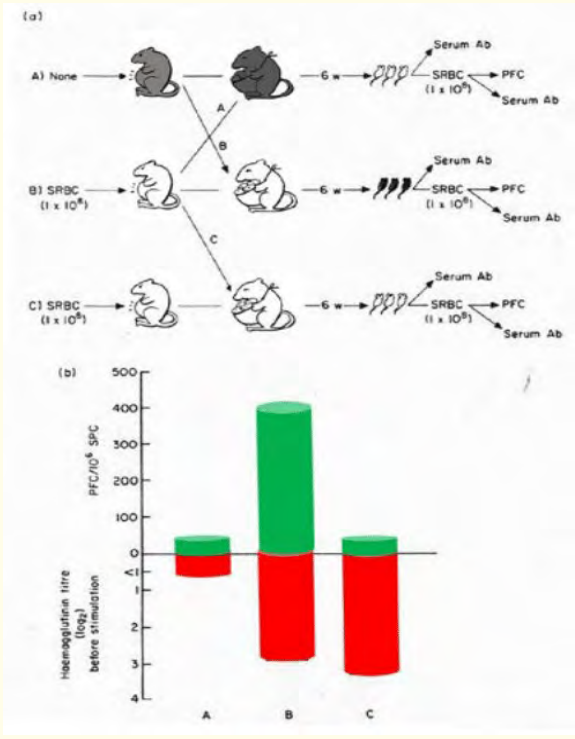

Figure 2: *Effect of Maternal antigenic stimulation on the active immune responses in her young-the foster mother experiment in the experimental and control group.*

During pregnancy, the same stage of mother mice were divided in to two groups. The one group was administered SRBC (experimental group) and other was only physiological saline (control group). The two group of baby mice were mutually exchanged and brought up to 8 weeks. And then active antigen stimulation were carried out for each group of mice.

Transferred effective cells were MHC restricted to her young

So as to understand this bias from mother to her young, we moved further to clarified, this biological significance of this phenomenon, employing more natural system to test the transfer of antigen or antibody the foster mother experiments were designated. One group received antigenic stimulation and the other did not. On the day of birth, the young of both group were exchanged each other [28,29]. So

as to confirm the immune responsiveness of young mice, all the mice were injected 5 x 10^8 of corresponding antigen SRBC for induction to good immune response to SRBC. The results are as follows; the offspring nursed by the mothers in the control group but delivered by mothers in the experimental group did not respond to further SRBC stimulation. On the other hand, the offspring nursed by the experimental mother but delivered by the normal mother responded well to further SRBC stimulation. Nevertheless, the passive maternal antibody in her baby, they did respond to further active antigenic stimulation [26,30-49].

MHC-restriction of T cell is necessary to this suppression

The question arises to whether the maternal bias was standard immune mechanism ruled in or not. In order to confirm genetic back ground of this biological significance, back cross experiment was planned to assess this phenomena. As shown in figure 3, back cross system was made to separate child mice as different genetic expression on cell surface. Above experiments implied that T cells of the same subtype of were effector cells in both mother and her young. Moreover, maternal cell may be difficult to cross the anatomical barrier between mother and her young. With an anatomical stand point of view in immunological view, more than 200,000 mw of material could not enter into her baby. So, the cell, lymphocyte cannot imagine to-cross the border. There was a legend to need cell to cell contact between the cells participating antibody secretion/production [50-54]. The mechanism of suppression still unclear, so we further tested MHC-restriction suppression in this model [41,44,55-58]. C57BL/6J(H-2b) pregnant mice were intraperitoneally injected with 5 × 10^8 SRBC/mouse on day 10 - 12 of gestation. Five days later, maternal T cells were obtained from the spleen of the immunized pregnant mouse and were adoptively transferred into the normal pregnant mice of (C_3H/HeJ × C57BJ/6J) F_1 on day 10 - 12 of gestation. The recipient mice had been back crossed with C_3H/HeJ male mice. The H-2 haplotype were expected from backcross experiment were H-$2^{b/b}$ and/or H-$2^{b/k}$. The babies were kept in a specific pathogen free: SPF system up to 6 weeks after birth. Suppression of the anti-SRBC IgG-PFC responses was detected only in the offspring of H-2^{bxk} but not in those of H-2^{bxb}. In this backcross system for identified the materno-fetal relation in immunological cell level, C_3H/HeJ male mouse was used as control. The PFC response was compared between the controls and the offspring of the recipient with the same haplotype. Reverse results were obtained in a reverse backcross mating pattern [59-62]. On the 12 days of gestation, pregnant C_3H/HeJ mother was immunized by SRBC. T cell were kept from spleen and passively injected (C_3H/HeJ × C57BL/6J) F_1 pregnant mice, prepared back crossing. The suppression of anti-SRBC PFC responses was found only in the H-2^{bxk} offspring among (C_3H/HeJ × C57BL/6J) F_1 × C57BL/6J from (C_3H/HeJ × C57BL/6J) F_1 recipients [60]. These results implied that this maternal bias between mother to her baby dependent upon the regular immune induction mechanism, MHC restriction in cell to cell contact.

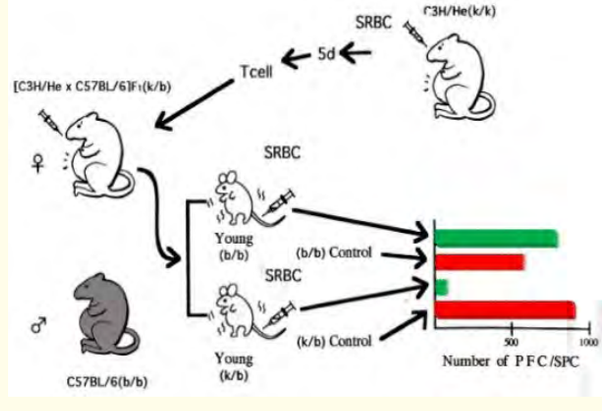

Figure 3: *MHC restriction between mother and her young.*

In order to test MHC restriction between mother to her young about this immune suppression, C3H/He (k/k) and C57BL/6 (b/b) mouse were mated (F1; k/b) and then backcrossed by C57BL/6 male mouse, then given F2 mice that consisted with two different type of group, F2 (b/b) and F2 (k/b). F1 female mother was adoptively injected with educated T-cells derived from C3H/He pregnant mice that was immunized with SRBC prior to cell transfer. All of the F2 mice were immunized with corresponding antigen and then developed PFC. As indicated in Figure, only the F2 mice that was express (k/b) haplotype suppressed, but not in (b/b) haplotype.

Maternal Lymphocyte Trafficking

With our series of experiment, mother lymphocyte did traffic to her baby through placental barrier. Following was the direct trial for probed the cell trafficking to her baby. The key factor contributed in this suppression was not antigen selected nor the specific antibody produced. However, CD4 lymphocyte mas the key factor in both pregnant mother and her baby. Therefore, MHC-matching was necessary between the cells concerned. MHC restriction in cell to cell interaction is usually cognate interaction system [60]. With classical content of Biology, maternal cell could not her placenta, only IgG immunoglobulin that was 200,000, mw could as the member immune mechanism. Wan reported that mother cells could transfer to her fetus and also in the case between fetus to fetus transmission. However, from gene analysis experiment, Wan showed that mother lymphocyte across the barrier to her offspring [61,62]. The combination and MHC type and experimental design was shown in the figure 3. A genetic marker and test protocol was shown in figure 3, in order to show the maternal cell trafficking by genetic engineering. For the purpose of this trial, the class II Eb gene was focused which was found in H-2 allele of rodent. The DNA polymorphic analysis was selected to show the maternal H-2 alleles in the lymphoid organ of baby mice. From this gene analysis, maternal T cell proved to traffic into her baby.

Atopic allergy in the young is possible mother cell act in her young as it was heritage

The purpose of this paper is to propose evidence-based proposition to prevent atopic allergy in human. The answer is possible according to our series of studies in rodents. The genetic and environmental factors lead to the emergence of allergen reactive T lymphocytes [63]. The most effective prevention is to avoid risky combination between female and male. So as to find a risky combination is the same method and grade of sensitivity that the matching test of donor/recipient routinely issued in organ transplantation. But, it may not so easy to avoid the risky paring especially in mankind.

Discussion

An Allergic response was increase along with developed country where public health system were systematically developed. A developing countries on the other hand, the incidence of allergic response had been few. This phenomenon suggested to maintain polyclonal IgE responsiveness in such circumstances. The listed alleges were many as the botanical and animal. The purpose of this report was formulated to clarify the materno-fetal relation to the immune system during pregnancy for sorting out for atopic allergy. The test system were mainly designed for the inbred mouse in order to clarify the genetic background of inductive and effector cells in allergic response. In general consideration, a mother would like to deliver her baby in safe. However, is it possible the allogenic relation between mother and her baby? In this report, we first set up mother and her baby in syngeneic relation. In such a combination the maternal bias was evident in her baby. This suppression was the case in 1/6 of life-span of rodents, including mice, rats and guinea pigs. If it may possible to expand mouse systems into humans, the suppression is affect about until 13 years-old. Including above implications, this phenomenon is serious and worthy of future investigation if suitable test scheme is accepted/available in human. Even in some difficulties, we could hope that this maternal bias was some lights to her young avoiding atopic allergy [64].

Conclusion

1. Maternal immune response during pregnancy induced complete bias to her young.
2. Effective timing to induced the bias was five days after fertilization and three days before delivery in rodent.
3. Active bias to her young was good for 1/6 of life span.
4. Transferred lymphocytes were MHC restricted to her young.
5. Maternal Lymphocyte Trafficking to her young.
6. Atopic allergy in human young is possible that mother cell act in her young as it was heritage.

Conflict of Interest

We declared non for these studies.

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