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REVIEW

The *B* Complex in the Chicken

——Development from a blood group system into the major histocompatibility complex——

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Abstract The major histocompatibility complex (MHC) in chickens was initially described as a blood group locus called the B system. Early studies on the B blood group system revealed that the B system was associated with some physiological functions. Subsequently, it was found that the B system was associated with several immunological functions and should be the MHC in chickens. Then, the system is now called the *B* complex. The *B* complex is composed of three regions, *B-G*, *B-F* and *B-L*, and regulates a number of functions similar to those found in mammalian MHC. The DNA structure of each region within the *B* complex is now gradually becoming clear.

Key Words: major histocompatibility complex, blood group, chicken, disease resistance

INTRODUCTION

Erythrocyte alloantigens in chickens were first described by LANDSTEINER and MILLER (1924). After that, studies on chicken blood groups were carried out by several researchers (TODD, 1930; KOZELKA, 1933; HAYASHIDA, 1942), although most of them paid attention only to individual differences. Concerning the inheritance of erythrocyte antigens, THOMSEN (1934, 1936) first showed that most antigens were inherited as dominant characters.

Detailed studies on chicken blood groups were given by BRILES *et al.* (1950). They found 12 erythrocyte antigens by alloimmunization and showed that these antigens were genetically controlled by two loci named *A* and *B*. Additional blood group loci were also reported by GILMOUR (1959), BRILES (1962) and CRITTENDEN *et al.* (1970). At present, 12 blood group systems, A, B, C, D, E, H, I, J, K, L, P and R, are known.

Out of these blood group systems, the B system has been paid special attention due to its effects on some physiological functions. As early as the identification of the B system, it was noticed that the *B* locus had heterozygotic effects upon fitness (SHULTZ and BRILES, 1953). The results were confirmed by subsequent studies (BRILES *et al.*, 1957; OKADA and MATSUMOTO, 1962). On the other hand, SCHIERMAN and NORDSKOG (1961) found that the *B* locus was not only a blood group locus, but also a locus controlling skin graft rejection. The fact that B antigens are histocompatibility antigens was also confirmed by JAFFE and MCDERMID (1962), using the graft-versus-host reaction (GVHR). Some ten years later, it was shown that the *B* locus controlled immune responses (GÜNTHER *et al.*, 1974) and the mixed lymphocyte reaction (MLR) (MIGGIANO *et al.*, 1974). All these studies provided evidence that the *B* locus

is the major histocompatibility complex (MHC) in chickens comparable to the *H-2* in mice and the *HLA* in humans.

In 1976, Hála *et al.* found a case of crossing-over within the *B* locus. On the bases of studies on this recombinant gene, Pink *et al.* (1977) presented a three-locus model for the *B* complex; *B-F, B-L* and *B-G*. The B-F and B-L antigens are comparable to class I and class II antigens in mammals, respectively. The B-G antigens were named class IV, since no comparable antigens are found in mammals (Simonsen *et al.*, 1982).

The purpose of this review is to present an overall view on development of studies on the *B* complex in chickens.

NOMENCLATURE OF THE *B* COMPLEX

Alleles at the *B* locus were first described with superscripts of *B* showing the shared blood factors, using the same system as the nomenclature of blood groups of cattle and other domestic animals (Briles *et al.*, 1950). However, the increase in the number of shared blood factors and the use of unabsorbed polyvalent reagents made this nomenclature unwieldy (Okada and McDermid, 1970). Briles *et al.* (1957) introduced a new terminology in which *B* alleles were numbered serially, B^1 to B^n.

However, this method introduced another confusion, because several laboratories adopted the same serial numbers for their own, but different, *B* alleles. To resolve this confusion, comparison tests between laboratories were carried out from the 1960's to the early 1970's (Okada and McDermid, 1970; McDermid and Oosterlee, 1972). However, these endeavors were not successful.

In mice, the nomenclature of H-2 system is based on inbred lines sharing antigens. Such a system reduces the confusion described above. In 1982, Briles *et al.* tested *B* haplotypes of 27 inbred or partially inbred lines of chickens, and then those were internationally accepted as reference sources for the 27 distinct standard *B* haplotypes. Furthermore, the designation system for recombinant haplotypes was also proposed. The designation consists of the number of the *B-F* allele present, followed by the letter *r* and a number indicating the order of a recombinant of the particular B-F allele.

This nomenclature system, however, does not solve yet the difficulty of identifying *B* alleles in non-inbred chicken populations. Blood typing reagents prepared in a closed population could not be easily used due to their crossreactivity for typing chickens from genetically different populations.

Recent analyses of *B* haplotypes by restriction fragment length polymorphism (RFLP) suggested some possibilities of solving this problem (Miller *et al.*, 1988). Kuragaki *et al.* (1991) also analyzed RFLP patterns of *B* haplotypes from different lines using a probe for the *B-G* region of *B* complex. The RFLP pattern showed good correlation with the *B* haplotype. They concluded that RFLP analysis would be a useful means for identifying *B* haplotypes of chickens. On the other hand, subdivision of a serologically defined *B* haplotype by RFLP pattern has been also observed by Chaussé *et al.* (1989). They subdivided the B^{21} haplotype into 5 subtypes by RFLP patterns of *B-F* and *B-L* regions. Thus, additional studies with more restriction enzymes will be necessary to establish the standard RFLP pattern for each *B* haplotype.

BIOLOGICAL CHARACTERISTICS OF THE *B* COMPLEX

Heterozygosity at the *B* locus

In early studies of the B blood groups, the existence of numerous multiple alleles even in inbred lines led to the idea that the *B* alleles were in some way associated with physiological function related to survival. As early as 1953, SHULTZ and BRILES pointed out the heterozygosity of inbred lines at the *B* blood group locus. Later, using 73 closed non-inbred and inbred lines, BRILES *et al.* (1957) found that segregation of alleles at the *B* locus occurred in at least 71 of 73 lines tested. GILMOUR (1959) also found such segregation in highly inbred lines at 7 blood group loci including the *B* locus.

Direct evidence of selective advantage of heterozygotes at the *B* locus was presented by OKADA and MATSUMOTO (1962). By a selection experiment they found that the observed frequencies of heterozygotes at the *B* locus were higher than the expected frequencies and artificial selection for egg production further raised the proportion of heterozygotes. However, the superiority of heterozygotes was not consistently demonstrated for any single character.

On the other hand, BRILES and ALLEN (1961) compared two homozygotes; B^1B^1 and B^2B^2. B^1B^1 had a greater juvenile livability than B^2B^2, but the situation was reversed in the adult period. They suggested that the alternation of superiority among genotypes during the life span might lead to heterozygote superiority.

Concerning association of particular characters with the superiority of heterozygotes, MORTON *et al.* (1965) found overdominance effects of *B* genotypes on the livability in the incubation period. FUJIO (1971) also found that the hatchability of heterozygotes was markedly higher than that of homozygotes, and suggested that hatchability was the most important factor for the maintenance of stable polymorphism at the *B* locus. On the other hand, NORDSKOG *et al.* (1973) analyzed two synthesized populations segregating four *B* alleles. The B^1 homozygote was consistently lowest in egg production and highest in adult mortality. They concluded that the superiority of heterozygotes was mainly a consequence of poor fitness of the B^1 homozygote.

All of these cumulated data present evidences that polymorphism at the *B* locus is maintained by the selective advantage of heterozygotes.

Association of *B* alleles with production characters

Findings on heterozygotic effects at the *B* locus also stimulated investigations on possible relationships between *B* alleles and production characters. ALLEN and GILMOUR (1962) compared the effects of the *B* genotypes, $B^{13}B^{21}$ and $B^{14}B^{21}$, on hatchability, juvenile and adult viabilities, and egg production. The effects of *B* genotypes were observed on these traits excluding hatchability. The selective advantages of $B^{14}B^{21}$ over $B^{13}B^{21}$ were represented with a selection coefficient of about 0.2. The unfavorable effect of the B^{13} allele on egg production was also observed by PAPP (1968).

Using crossbred populations, ALLEN (1962) pointed out the significance of the interaction between *B* alleles and background genotype in variation of production characters. GILMOUR and MORTON (1970) studied the association of ten possible *B* genotypes with mortality during incubation. The effects of *B* genotypes were different by population. MCDERMID (1965, 1966) also tested the effects of *B* genotypes on mortality, body weight, egg weight and egg pro-

duction, and found that the effects of *B* genotypes varied for each flock or for each experiment.

Okada *et al.* (1966) measured five production characters in two non-inbred lines and their crosses. Significant effects of *B* alleles were found in only 5 of 82 comparisons. The proportion of variance controlled by *B* alleles was as small as 1 or 2 percents. They suggested that it would be not economical to incorporate *B* genotyping in a breeding program. Hardin (1971) also tested the relationship between *B* alleles and economic traits in non-inbred meat-type chickens. Although significant differences were observed in some of the comparisons, no consistent differences were observed over a period of years.

On the other hand, Hansen and Law (1970) transferred B^2 allele by repeated backcrossing from a inbred line H1 (*B* genotype B^2B^2) to another inbred line H36 ($B^{14}B^{14}$). After six backcrosses and subsequent segregation of B^2B^2 homozygotes, a new line H18 (B^2B^2), which has the same genetic background as H36 except the *B* genotype, was established. The adult livability of the H18 line was almost the same with the H1 line and superior to the H36 line, indicating that the B^2 allele significantly reduced adult mortality. On the basis of observation over a five-year period, Nordskog *et al.* (1973) also found that the B^2 and B^{21} alleles had favorable effects on egg production and adult mortality but the B^1 allele had unfavorable effects.

Summing up these accumulated data, it can be concluded that although associations were found between *B* alleles and production characters, most of them seemed to be too small for practical use in animal breeding.

IMMUNOLOGICAL FUNCTIONS OF THE *B* COMPLEX

Transplantation

In early days, studies on histocompatibility antigens were carried out through approaches such as induction of tolerance due to erythrocyte injection (Cannon *et al.*, 1958). However, such studies were not effective in finding any specific transplantation antigen.

Evidence that the B blood group antigens were also histocompatibility antigens was first presented by Schierman and Nordskog (1961). They carried out reciprocal skin grafting between 16-day old chicks of inbred lines having known *A, B, D* and *L* blood group genotypes. Skin grafts exchanged between B-incompatible chicks were rejected within 12 days, whereas grafts between B-compatible chicks survived through 40 days post-operations. The other systems had no effects.

This finding was soon confirmed by several investigators. Craig and McDermid (1963) observed the importance of the *B* blood group locus for histocompatibility effects in young chicks. Furthermore, they showed that skin graft survival was affected by the total number of antigenic factors not shared by the host. Gleason and Fanguy (1964) also exchanged skin grafts between 7-day old full-sib chicks. All grafts from B-incompatible donors were rejected during the 10-week observation period, but about 67% of B-compatible grafts survived throughout the observation period.

In the A, D, E and L systems, no differences were observed between the compatible and incompatible grafts (Schierman and Nordskog, 1961; Gleason and Fanguy, 1964). Especially, no relation of the *A* locus to histocompatibility was demonstrated using

syngeneic lines (HÁLA *et al.*, 1966).

HASEK *et al.* (1966) and HÁLA *et al.* (1966) established syngeneic lines by brother×sister matings within highly inbred lines using identity in transplantation and erythrocyte antigens. Using these syngeneic lines and their crosses, HÁLA (1969) estimated that these lines differed from each other at 3 to 13 histocompatibility loci. The effect of minor histocompatibility loci was also confirmed by comparing full-sibs to half-sibs on survival time of B-compatible grafts (YAMAMOTO, 1975). Recently, YAMAMOTO and OKADA (1990) showed the effectiveness of selection on survival time of allografts within the same *B* genotypes.

Graft-versus-host reaction

Although skin grafting is very useful for identifying histocompatibility antigens, it necessitates a long observation period. Another useful means for identifying histocompatibility antigens is graft-versus-host reaction (GVHR), which was first discovered by SIMONSEN (1957). Using inbred lines and their crosses, JAFFE and PAYNE (1962) showed that one major and several minor histocompatibility antigens caused splenomegaly in GVHR. This major histocompatibility locus was identified as the *B* locus, using the donor-host relationship of known *B* blood group genotypes (JAFFE and MCDERMID, 1962). The results were also confirmed by SCHIERMAN and NORDSKOG (1963).

Although GVHR is mainly caused by donor-host differences at the *B* locus, it was also found that the degree of splenomegaly was affected by several factors such as the age of the donor (SETO, 1968), sex of the donor or host (SOLOMON, 1961) or genetic strains (JAFFE and PAYNE, 1962).

Differences due to donor's *B* alleles in the degree of splenomegaly were first reported by MIKAMI *et al.* (1969). They found that the degree of splenomegaly was affected by the *B* alleles of the donor. The degree of splenomegaly was in order of $B^A > B^I > B^G$. The results were also confirmed by FUJIO (1970) and LONGENECKER *et al.* (1972). Although genetic variation of donor competences in GVHR were mostly due to the *B* alleles of donors, effects of minor genes were also observed (OKADA and MIKAMI, 1974). They selected chickens for high and low donor competences in splenomegaly and established two different GVHR-lines. The average realized heritability over three generations was 0.41.

Although GVHR is expressed by immunological reaction of donor lymphoid cells to the recipient's antigens, studies on sex chromosomes revealed that the recipient cells also participate in the spleen enlargement (JAFFE and FECHHEIMER, 1966). The recipient's competence in splenomegaly was also affected by *B* locus alleles (OKABAYASHI and OKADA, 1976). The effect of *B* alleles in the recipient was parallel to that in the donor. OKADA (1982) studied the comparative contribution of the donor and recipient in the degree of splenomegaly. It was shown that the effect of *B* alleles was greater in the recipient than in the donor, although minor gene effects were greater in the donor than in the recipient. On the other hand, OKADA *et al.* (1987) conducted parabiosis between embryos of strains having different GVHR competences. They showed that the GVHR competence of parabionts between different *B* genotypes was changed in the direction of the competence of the partner.

Concerning the region within the *B* complex controlling GVHR, LEE and NORDSKOG (1981) compared the relative importance of blood group and immune response (*Ir*) regions of the *B* complex. The results suggested that the *Ir* region played a significant, but minor role

compared with the serologically identified *B* locus.

Immune responses

Studies on genetic control of immune response have revealed that *Ir* genes are also closely linked to the *B* locus as similar to MHC in mammals. Günther *et al.* (1974) reported that responsiveness to synthetic polypeptide poly(Tyr, Glu)-Ala-Lys ((T, G)-A--L) was linked to the *B* locus. Balcarová *et al.* (1974) also showed that *B* alleles were associated with differences in antibody response to the dinitrophenyl group (DNP) conjugated to chicken γ globulin (CGG). The MHC-linked immune responses to other antigens have also been confirmed by Pevzner *et al.* (1975).

In the immune response to poly (Glu, Ala, Tyr) (GAT) or (T, G)-A--L, it was found that high immune responsiveness was genetically dominant to low responsiveness (Benedict *et al.*, 1975; Koch and Simonsen, 1977). On the other hand, Okabayashi and Okada (1977) found that the immune responsiveness to goat erythrocytes (GRBC) was parallel to the splenomegaly competence in GVHR. The relative immune responsiveness of *B* genotypes was $B^{11}B^{11} > B^{9}B^{11} > B^{9}B^{9}$. Similar results were also obtained in the immune response to DNP-CGG, suggesting that the action of the *B*-linked *Ir* gene is additive or incomplete dominant (Yanagimoto and Okada, 1980). However, recent studies using DNP-human globulin showed that high antibody responsiveness to DNP was controlled by a dominant gene (Loudovaris *et al.*, 1990). Differences between these studies might be caused by the genetic background of the lines used, or by differences in immunogenecity of antigens as shown by Koch and Simonsen (1977).

On the other hand, Benedict *et al.* (1977) found antigen-specific genetic control of the immune response. Low responders to GAT were high responders to GAT conjugated methylated bovine serum albumin (MBSA-GAT), whereas high GAT responders were low responders to MBSA-GAT. Similar results were also reported by Pevzner *et al.* (1979) and Okabayashi and Okada (1989). It was shown that the relative immune responsiveness of each *B* genotype was different due to the antigens used for immunization.

It has also been reported that differences in immune responses are associated with the class of immunoglobulins. Benedict *et al.* (1975) reported that the *B* gene difference in responses to GAT was due to 7S antibodies. On the contrary, Okabayashi and Okada (1977) showed that the *B* genotype difference in immune response to GRBC was mostly due to IgM antibodies and the line difference was due to IgG antibodies.

Evidence suggesting a crossing over between the region coding for erythrocyte antigens and the region controlling immune response was obtained by Pevzner *et al.* (1978). However, no serological evidence indicating that this *Ir* region corresponds to the *B-L* region has been shown. Recently, evidence on association of the *B-L* region with immune response was presented by Uni *et al.* (1990), using RFLP analysis with a B-L probe.

Cell cooperation and other functions

The role of MHC antigens on T cell-B cell cooperation in the immune response of chickens was first reported shortly after the initial discoveries in mice. Toivanen *et al.* (1974a, b) transplanted bursal stem cells taken from age-matched normal donors into the cyclophosphamide-treated chicks, and produced chimera chickens having donor-derived B cells and host-derived T cells. In the presence of full identity at the MHC antigens,

the chimera chickens produced antibodies. However, if the identity was lacking, antibody production was not observed except for the thymus independent antigens.

Later findings of recombinant *B* alleles made it possible to study the function of each region within the MHC. Using such recombinant *B* alleles, VAINIO *et al.* (1984) showed that antibody production to the thymus dependent antigens required the identity of class II (B-L) antigens between T and B cells. Thus, B-L antigens served as a restriction element in T-B cell cooperation.

MHC restriction was also observed in the process of antigen presentation to T cells by macrophages. In the process, B-L antigens were also found to serve as a restriction element in antigen recognition by T cells (VAINIO *et al.*, 1988).

The total hemolytic complement level was found to be determined by a dominant gene associated with the MHC (CHANH *et al.*, 1976). The association of complement levels with *B* alleles was also confirmed by OKADA (1980) and MASHIMA *et al.* (1991). On the other hand, KOCH (1986) reported that the complement component factor B in chickens was not linked to the MHC, differing from mammalian species in which it was found the close linkage of factor B with the MHC.

The "adjuvant effect" of the B-G antigen was found in the production of antibodies to B-F antigens. The production of B-F antibodies required the co-presence of the B-G antigen, whereas antibodies to B-G antigens were formed regardless of the presence or absence of the B-F antigen (HÁLA *et al.*, 1981b).

DISEASE RESISTANCE AND THE *B* COMPLEX

Marek's disease

Early studies on the relationship between disease resistance and the *B* alleles were mostly concerned with general viability, but not with resistance to a specific disease. Clear evidence of the effect of a specific *B* allele on mortality was observed by HANSEN and LAW (1970), using a congenic line of chickens with regard to the *B* allele.

The first evidence of the association of *B* alleles with specific disease resistance was found in Marek's disease (MD). In a flock of chickens suffering from severe outbreak of MD, BRILES (1974) observed a highly significant deficiency of the B^1 allele in the progeny from B^1B^6 or B^1B^7 sires. OKADA *et al.* (1977) analyzed changes in polymorphic gene frequencies over five generations in seven strains of chickens selected for MD resistance. The frequencies of the blood group A^6 and B^8 alleles showed a consistent trend of increase, whereas the frequency of B^{11} allele gradually decreased. Especially, the frequency of the B^8 increased in proportion to the selection intensity to MD resistance, suggesting a strong association between the B^8 allele and MD resistance.

LONGENECKER *et al.* (1976) compared MD mortality among several *B* genotypes, and found that chicks carrying the B^{21} allele were more resistant to MD than the B^2, B^{14} or B^X alleles. The association of the B^{21} allele with MD resistance was also confirmed by BRILES *et al.* (1977).

On the other hand, PAZDERKA *et al.* (1975) reported that the *B* alleles associated with MD resistance generally have low GVHR competence. LONGENECKER *et al.* (1975) suggested that B-associated resistance with low GVHR might be attributed to the restraint of proliferation

of T cells, which are the target cells of the MD virus. If the hypothesis is true, it leads to an idea that selection for low GVHR competence may bring out the resistance to MD. Okada and Mikami (1974) established, by selection, two lines having high (H) and low (L) GVHR competences. Using these two lines, Ashikaga *et al.* (1984) tested the association between GVHR competence and MD resistance. Although the GVHR-L line seemed to be more resistant than the GVHR-H line, the line difference was very small. Furthermore, highly significant interaction between the GVHR line and the *B* genotype was found. They suggested that the association of low GVHR competence with MD resistance, if there is any, may be small. On the other hand, Yamamoto *et al.* (1991) tested the resistance to transplantable MD lymphomas, using the same GVHR-selected lines. Although significant line difference was observed, the difference in tumor resistance between *B* genotypes was not significant.

Interrelationship between immunocompetences and MD resistance was examined by Tamaki (1981) and Okada and Yamamoto (1987), using lines of chickens selected for high and low IgG levels at 10 weeks of age. It was found that the IgG-L line was more resistant to MD than the IgG-H line.

During the course of selection for high and low immune response to *Salmonella pullorum*, Pevzner *et al.* (1981) subdivided *B* alleles into two parts; one identified by blood typing and the other identified by immune response to GAT. Both B^1B^1 GAT-H and $B^{19}B^{19}$ GAT-H chickens were more resistant to MD than both B^1B^1 GAT-L and $B^{19}B^{19}$ GAT-L birds, suggesting that the region of the *B* complex controlling MD resisitance would be the *Ir* (*B-L*) region.

On the other hand, Briles *et al.* (1983) also analyzed MD resistance, using a recombinant allele within the *B* complex, $B^{F21\text{-}G19}$, consisting of a *B-F* segment from B^{21} and a *B-G* segment from B^{19}. MD resistance of $B^{F21\text{-}G19}B^{19}$ heterozygotes was higher than $B^{19}B^{19}$, but was almost equivalent to $B^{19}B^{21}$. Thus, the *B-F* region or closely linked region to the *B-F* was presumed to be responsible for MD resistance.

Rous sarcomas

Resistance to tumor induced by Rous sarcoma virus (RSV) was also found to be associated with *B* alleles. Schierman *et al.* (1977) and Collins *et al.* (1977) found that RSV-induced tumors grew consistently in one strain of chickens and regressed in the other strain. By crossing such two strains, they showed that regression of RSV-induced tumors was a dominantly inherited trait controlled by a gene within or closely linked to the *B* complex.

Heinzelmann *et al.* (1981a, b) inoculated lymphocytes from B^5B^5 chickens with progressing RSV-induced tumors into B^2B^2 chickens having ability to resist tumors. The inoculation brought out the progression of tumors in the B^2B^2 chickens. Futhermore, crossreactions between the B_5 antigen and a tumor-associated antigen were observed. They hypothesized that progression of RSV-induced tumors in B^5B^5 chickens might be induced by unrecognition of the tumors as foreign.

Similar to MD resistance, the region controlling regression of RSV-induced tumors was found to be closely linked to the *Ir* region of the *B* complex (Gebriel *et al.*, 1979). In addition to the *Ir* region, it was suggested that the *B-F* region might also play an important role in the regression of tumors (Gebriel and Nordskog, 1983). Similar results were also obtained

by PLACKY and BENDA (1981).

The MHC genes were also associated with the incidence of metastatic tumors. COLLINS *et al.* (1977) found that the percentage of birds with metastases was higher in B^5B^5 than in B^2B^2 and B^2B^5 birds. In subsequent experiments using the same flock (COLLINS *et al.*, 1986) and crossbreds with New Hampshire chickens (COLLINS *et al.*, 1985), high metastases in B^5B^5 birds were confirmed, although non-MHC genetic effect(s) on metastasis were also suggested by the line differences found in the B^5B^5 chickens.

Other diseases

Susceptibility to lymphoid leukosis seemed to be also associated with the *B* complex. BACON *et al.* (1981b) reported that inoculation with RAV-1 lymphoid leukosis virus caused death due to erythroblastosis and the mortality was significantly higher in B^5B^5 than in B^2B^2 or B^2B^5 chickens. The B^5B^5 birds were also susceptible to MD and Rous sarcomas. They suggested that some gene(s) in the *B* complex may determine a general ability to resist tumor formation.

The Obese strain (OS) of White Leghorn chickens develops circulating autoantibodies to thyroglobulin and lymphocytic infiltration of their thyroids during aging. The susceptibility of OS chickens to this autoimmune thyroiditis was closely associated with the *B* genotypes. BACON *et al.* (1974) reported that B^1B^1 and B^1B^4 chicks were more susceptible to the early onset of thyroiditis than their B^4B^4 siblings. In further experiments ROSE *et al.* (1976) found that the mean hemagglutinating antibody titer to thyroglobulin was significantly higher in B^1B^1 and B^1B^4 chicks than B^4B^4 chicks. They suggested that the *Ir* gene region within the *B* complex might be responsible for susceptibility to spontaneous autoimmune thyroiditis. Furthermore, analysis of the effects of family and *B* haplotype revealed that interaction of the *B* haplotype with genes at non-*B* loci was also important (BACON *et al.*, 1981a).

Genetic resistance to fowl cholera (LAMONT *et al.*, 1987) and coccidiosis (CLARE *et al.*, 1985) was shown to be linked with the MHC. It was suggested that the resistance to coccidiosis was also influenced by interaction of MHC and non-MHC genes (LILLEHOJ *et al.*, 1989). On the basis of changes in frequencies of *B* alleles in lines selected for the antibody titer to *Leucocytozoon caulleryi*, OKADA *et al.* (1988) suggested the association of the *B* alleles with the resistance to leucocytozoonosis.

STRUCTURE AND FUNCTION OF THE *B* COMPLEX

Structure of the *B* complex

Chromosomal location of the *B* complex was studied by BLOOM and BACON (1985). The *B* complex was on the micro-chromosome ranking about 16th in size, and linked to the ribosomal RNA genes that were detected as a nucleolar organizer region (BLOOM *et al.*, 1987).

As described above, the *B* complex is composed of at least three regions, *F*, *L* and *G*, which code the class I, class II and class IV antigens, respectively. Searches for recombinant *B* haplotypes have been performed by serotyping chickens from appropriate matings (VILHELMOVÁ *et al.*, 1977; KOCH *et al.*, 1983; HÁLA *et al.*, 1988). Although several recombinants were identified, all of them were recombinants between *B-G* and *B-F* regions. The distance between the *B-G* and *B-F* regions was estimated to be about 0.05 centimorgans

(Crone and Simonsen, 1987). Although extensive searches for recombination between the *B-F* and *B-L* regions were carried out, no recombinants were found between the *B-F* and *B-L* regions.

Recent molecular studies have revealed the close proximity of the *B-G*, *B-F* and *B-L* regions. Although the total size of the *B* complex is not yet known, the *B-G* region covers at least 600kb and contains numerous *B-G* genes. On the other hand, minimal size for the *B-F/L* region was estimated about 320kb (Guillemot *et al.*, 1988, 1989). In the *B-F/L* region, a total of six *B-F* and five *B-Lβ* genes have been found. These *B-F* and *B-L* genes are intermingled in the *B-F/L* region (Kroemer *et al.*, 1990). This is different from mammalian MHC, where class I and class II genes are organized separately in distinct regions.

B-G antigens encoded by the *B-G* region were considered so far to be expressed exclusively on cells of the erythrocyte lineage (Crone and Simonsen, 1987). Recently, it was learned that B-G antigens are expressed on cells in many different tissues including cells of the immune system (Miller *et al.*, 1990; Salomonsen *et al.*, 1991). The B-G antigens are highly polymorphic antigens with molecular weight of 40, 000 to 48, 000 under reduced conditions. In unreduced conditions, the antigens appeared as dimers of 85 to 90 kdaltons (Salomonsen *et al.*, 1987; Kline *et al.*, 1988b).

B-F antigens are present at the surface of the majority of somatic cells and of all peripheral blood lymphocytes and erythrocytes (Hála *et al.*, 1981a). The B-F antigens are considered as homologues of mammalian class I antigens. The antigens are composed of two polypeptide chains: one is glycoprotein with molecular weight of 40 to 44 kdaltons and the other is β_2-microglobulin of 11 to 12 kdaltons (Kline *et al.*, 1988a).

The B-L antigen is present on most of B lymphocytes, monocytes and macrophages, but not on unstimulated T lymphocytes (Hála *et al.*, 1981a). B-L antigens seem to be equivalent to class II antigens in mammals, and are composed of two noncovalently linked polypeptide, α and β chains. The molecular weight of α chain is 32 to 34 kdaltons and of β chain 27 to 30 kdaltons (Crone *et al.*, 19881; Guillemot *et al.*, 1986).

Functions of each region within the *B* complex

As described in previous sections, the functions of each MHC region are becoming clear through studies using recombinants within the MHC. Those functions of each region are summarized in Table 1.

Evidences that the *B-F* or its closely linked region regulated allograft rejection, GVHR and MLR had already been observed when the three-region hypothesis was presented (Pink *et al.*, 1977; Hála, *et al.*, 1977). On the other hand, Crone *et al.* (1981) reported that the B-L antigens elicited a strong reaction in MLR while B-F difference alone elicited only weak stimulation, and GVHR was also mainly controlled by B-L antigens. Pevzner *et al.* (1978) separated the region controlling immune response from the region for serologically determined antigens. Direct evidence of association of the *B-L* region with immune response was presented by Uni *et al.* (1990). Vainio *et al.* (1984, 1988) presented evidence that interaction between T cells and B cells or antigen-presenting cells was restricted by the B-L antigens.

There are several reports suggesting that the *B-F* or *B-L* region might play an important role in disease resistance (Briles *et al.*, 1983; Steadham *et al.*, 1987; Gebriel and Nord-

Table 1. Functions of each region within the MHC in chickens

Function	Region			References
	G	*F*	*L*	
Erythrocyte antigens	+	+	−	Pink *et al.* (1977)
Leucocyte antigens	+	±	±	Pink *et al.* (1977)
				Salomonsen *et al.* (1991)
Allograft rejection	+	±	?	Vilhelmová *et al.* (1977, 1987)
Graft-versus-host reaction	±	±	+	Crone *et al.* (1981)
				Lee and Nordskog (1981)
Mixed lymphocyte reaction	−	+	+	Crone *et al.* (1981)
Immune response	−	?	+	Uni *et al.* (1990)
T-B cell cooperation	−	−	+	Vainio *et al.* (1984)
Adjuvant activity	+	−	−	Hála *et al.* (1981b)
Marek's disease resistance	−	±	+	Briles *et al.* (1983)
				Steadham *et al.* (1987)
Rous sarcoma regression	−	+	+	Gebriel and Nordskog (1983)
				Collins and Briles (1984)

skog, 1983; Rose *et al*, 1976). However, it is not yet known which region of the *B-F* and *B-L* is more important, since no appropriate recombinants between the *B-F* and *B-L* regions have yet been found.

Concerning the *B-G* region, it was considered for many years to have no functions in immunological reactions (Crone and Simonsen, 1987), except for an adjuvant effect (Hála *et al.*, 1981b). However, recent studies have suggested that B-G antigens are also associated with immunological functions. Vilhelmova (1987) reported that graft survival time could be prolonged by prior induction of neonatal tolerance to the B-G product. Placky (1988) also found the effect of B-G antigens in GVHR. The degree of GVHR was significantly greater with the difference in the whole *B* haplotype (*B-F/L+B-G*) than with the difference in the *B-F/L* region only, although the *B-G* region incompatibility alone is not sufficient to elicit GVHR. These results suggest that the *B-G* region is also a histocompatibility locus.

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鶏における *B* 複合体

——血液型システムから主要組織適合複合体への発展——

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鶏の主要組織適合複合体は最初Bシステムと名付けられた血液型システムとして見出された。B血液型に関する初期の研究は，この血液型が生理機能と関連していることを示唆した。その後，Bシステムは種々の免疫機能にも関連していることが見出され，このシステムは鶏における主要組織適合複合体であることが判明した。そこで，このシステムは現在，一般にB複合体と呼ばれている。*B* 複合体は *B-G*, *B-F* および *B-L* と名付けられた三つの領域より成り，哺乳類の主要組織適合複合体と同様に，多くの機能に関与している。*B* 複合体の各領域の DNA レベルでの構造については，現在徐々に明らかにされてきている。

本論文ではB血液型から主要組織複合体への研究の発展過程と *B* 複合体に関する研究の現状について総説的に紹介した。

キーワード：主要組織適合複合体，血液型，鶏，抗病性